Churg-Strauss Syndrome with Neurologic Manifestations: Successful Treatment with Intravenous Immunoglobulins

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Churg-Strauss syndrome is a rare autoimmune disease, one of the antineutrophil cytoplasmic autoantibody-associated vasculitides. This disorder is characterized by multisystemic involvement including the presence of asthma, nasal and sinus disease, lung infiltrates, prominent peripheral blood eosinophilia, and necrotizing granulomas [1].

The pathogenesis remains largely unknown, as triggering factors for the development of CSS have not been definitively identified. ANCA, directed mainly against myeloperoxidase, are found in 40% of CSS patients at diagnosis and in patients with renal and peripheral nerve involvement but not cardiac disease [2]. Treatment of ANCA-associated vasculitides comprises the use of immunosuppressive agents (steroids, cytotoxic drugs). High dose intravenous immunoglobulins represent a promising treatment for non-responding patients. In this report we present the case of a patient suffering from asthma, allergic rhinitis and nasal polyposis who developed polyneuropathy, cutaneous manifestations and peripheral eosinophilia after her first pregnancy and was successfully treated with IVIG.

CSS = Churg-Strauss syndrome
ANCA = antineutrophil cytoplasmic autoantibody

PATIENT DESCRIPTION

A 34 year old woman with a past history of allergic asthma, nasal polyposis and sinusitis who had given birth 6 months earlier was referred to our department after being admitted to the emergency room. She presented with acute onset of low back pain, distal painful paresthesias of the legs, dysesthesia at the distal portion of the lower extremities, arthritis in both feet and ankles, and burning pain in both feet. These symptoms were followed by diffuse myalgia with muscular weakness involving primarily the lower extremities.

On admission, the patient was alert and well oriented; her temperature was 38.8°C and body weight 44.0 kg. In the previous 3 months she experienced significant weight loss, about 10 kg. A fine macular rash was visible on the face and the distal portion of the extremities. No wheezes or ronchi were heard in either lung. Vesicular murmur was diffusely harsh. No abnormalities were observed during the heart and abdominal examination. During the neurologic examination the following findings were noted: intact cranial nerve function, normal motor function in the neck and upper extremities, and severe distal muscle weakness in the legs together with hyporeflexia and hypoesthesia. Muscle tone of the lower extremities was reduced. The gait was markedly compromised because of the patient's painful paresthesias. The ankles were painful, red and swollen. When transferred to our department, the patient had already started therapy with hydromorphone 8 mg/day, gabapentin 1300 mg/day, pantoprazole 40 mg/day, methylprednisolone 60 mg/day and tramadol 100 mg/day. Laboratory analysis on admission to the emergency department showed white blood cell count 26,620 cells/µl, eosinophils 16,370/µl (61.5%), erythrocyte sedimentation rate 31 mm/hr, C-reactive protein 44 mg/L, creatine phosphokinase 419 UI/L, myoglobin 151 ng/ml, antinuclear antibodies 1:80 speckled, rheumatoid factor 253 UI/ml and perinuclear ANCA 86.9 IU/ml. Other autoantibodies tested were negative: cytoplasmic ANCA, antimitochondrial antibodies, anti-smooth muscle antibodies, anticardiolipin antibodies, anti-β2-glycoprotein 1 antibodies, anti-ds-DNA antibodies and anti-extractable nuclear antibodies. Also negative were quantiferon TB-gold assay and serologic tests for hepatitis B and C virus and cytomegalovirus.

During hospitalization the white blood cell count rose progressively to 62,780 cells/µl, with eosinophil count reaching 46,670 cells/µl (74.3%). We performed a FIP1L1/PDGRFα and *BCR/ABL* search, which was negative. Pulmonary computed tomography imaging showed subpleural nodularities, marked in the upper left lobe, and

IVIG = intravenous immunoglobulin

a pseudonodular image in the lateral segment of the right basal pyramid. CT scans of paranasal sinuses demonstrated mucosal thickening (soft tissue-like density) with subtotal opacification of all sinuses bilaterally. Brain magnetic resonance imaging and angiography were normal. Nerve conduction studies included motor and sensory conduction, late-response studies and needle electromyographic examination. Sural sensory nerve action potentials were reduced bilaterally, especially on the left side. Peroneal sensory nerve action potentials were absent bilaterally. Electromyography showed widespread denervation in both lower extremities, more evident in the right tibial muscle. The results of neurophysiologic studies were consistent with a symmetric severe sensorimotor polyneuropathy of the lower extremities that was compatible with vasculitic neuropathy.

Clinical and laboratory findings supported the diagnosis of CSS, meeting the American College of Rheumatology (1990) criteria. Histological investigations of a skin lesion demonstrated cutaneous necrotizing vasculitis with eosinophilic infiltrates. We administered high dose corticosteroid therapy (intravenous methylprednisolone 1 g/day for 3 consecutive days followed by prednisone 1 mg/kg/day) but the response was inadequate. After one month, cyclophosphamide was added (2 mg/kg every day), but the patient did not show any response during the following 6 months. It was therefore decided to administer five cycles of IVIG treatment (2 g/kg/month divided into five daily doses, for 5 consecutive months: Flebogamma® 5%, Grifols Italia, Italy), together with steroids and cyclophosphamide.

This combination of drugs was effective. Indeed, one month after the first IVIG treatment, the peripheral polyneuropathy had subsided markedly. Laboratory indexes and the patient's neurologic symptoms, such as myalgias, paresthesias and muscle weakness, showed considerable improvement. Electrophysiological examination showed an overall amelioration compared with the previous test. Electromyography revealed rare denervative elements at the left anterior tibial muscle. The patient gradually regained her normal weight and a sense of well-being. Laboratory tests after treatment showed white blood cell count 5170/µl, eosinophil count 380/µl (7.4%), normal ESR and CRP, and negative p-ANCA. Because of the rapid improvement in several indexes the dose of corticosteroids was tapered to a maintenance dose. Currently, 3 months after IVIG discontinuation, the patient is taking 15 mg of oral prednisone together with 50 mg cyclophosphamide daily, the disease activity is low and she reports that her quality of life is good. We will keep observing our patient to verify these good results.

COMMENT

Churg-Strauss syndrome is a rare autoimmune condition. Neurologic manifestations are often observed. Peripheral neuropathy is found in up to 75% of CCS patients, with predominant axonal involvement and frequent findings of mononeuritis multiplex, but peripheral polyneuropathy may also be present. Central nervous system involvement is less common and may include palsies of the cranial nerves (ischemic optic neuritis), cerebral hemorrhage or infarction, convulsions, coma, and psychosis [1]. Our patient experienced a symmetric severe sensorimotor polyneuropathy of the lower extremities. According to the literature, the initial management of CSS should include a high dose of steroids, 1 mg/kg daily, of prednisone or equivalent with tapering over 6 months. In patients with severe or rapidly progressing CSS, the administration of intravenous methylprednisolone pulse therapy at 1 g/day for 3 days is recommended. When corticosteroid therapy does not induce remission, or when patients have poor prognostic factors, immunosuppressive cytotoxic therapy is indicated [3]. However, patients with severe CSS could be resistant to conventional treatment.

IVIG therapy is a promising second-line treatment for CSS patients, particularly in the case of neuropathy [4]. With our patient, we started administering high dose corticosteroids combined with cyclophosphamide, but after 6 months an adequate response was not achieved and IVIG was therefore added. As early as 1 month after the first IVIG treatment the patient showed a remarkable amelioration of the peripheral polyneuropathy, and this good response has been maintained over time. Disease onset in our patient occurred 6 months after she gave birth. The relationship between CSS and pregnancy is still unclear, but a number of cases of pregnancy-related CCS treated with IVIG have been reported in the literature, with good outcome in peripheral nervous system involvement [5].

IVIG plays a role in modulating the immune system through several mechanisms including interference with the complement system and cytokine actions, neutralization of pathogenic antibodies, modulation of co-stimulatory molecules affecting the differentiation of T cells, dendritic cells and B cells, and suppression of autoreactive B lymphocytes. IVIG could have a neuroprotective effect. In CSS, IVIG should be considered for patients who experience non-response or severe adverse reaction to the standard treatments with immunosoppressive drugs, or in patients attempting and/or carrying a pregnancy. IVIG therapy has a good safety profile; in fact, most of the side effects reported are mild and transient, although the possible occurrence of severe adverse events such as throm-

ESR = erythrocyte sedimentation rate
CRP = C-reactive protein
p-ANCA = perinuclear ANCA

boembolic events and viral transmission cannot be excluded. We conclude that treatment with IVIG is a good and effective therapy for early-onset CSS and should be considered in patients with neurologic involvement and in patients with pregnancy-related CSS.

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Capsule

APJ acts as a dual receptor in cardiac hypertrophy

Cardiac hypertrophy is initiated as an adaptive response to sustained overload but progresses pathologically as heart failure ensues. Scimia et al. report that genetic loss of APJ, a G-protein-coupled receptor, confers resistance to chronic pressure overload by markedly reducing myocardial hypertrophy and heart failure. In contrast, mice lacking apelin (the endogenous APJ ligand) remain sensitive, suggesting an apelin-independent function of APJ. Freshly isolated APJ-null cardiomyocytes exhibit an attenuated response to stretch, indicating that APJ is a mechanosensor. Activation of APJ by stretch increases cardiomyocyte cell size and induces molecular markers of hypertrophy. Whereas apelin stimulates APJ to activate $G\alpha_i$ and elicits a protective response, stretch signals in an APJ-dependent, G-protein-independent fashion to induce hypertrophy. Stretch-mediated hypertrophy is prevented by knockdown of β-arrestins or by pharmacological doses of apelin acting through $G\alpha_i$. Taken together, their data indicate that APJ is a bifunctional receptor for both mechanical stretch and the endogenous peptide apelin. By sensing the balance between these stimuli, APJ occupies a pivotal point linking sustained overload to cardiomyocyte hypertrophy.

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Eitan Israeli

Capsule

Bacterial virulence proteins as tools to rewire kinase pathways in yeast and immune cells

Bacterial pathogens have evolved specific effector proteins that, by interfacing with host kinase signaling pathways, provide a mechanism to evade immune responses during infection. Although these effectors contribute to pathogen virulence, it was realized that they might also serve as valuable synthetic biology reagents for engineering cellular behavior. Wei and collaborators exploit two effector proteins, the *Shigella flexneri* OspF protein and *Yersinia pestis* YopH protein, to rewire kinase-mediated responses systematically both in yeast and mammalian immune cells. Bacterial effector proteins can be directed to inhibit specific mitogen-activated protein kinase pathways selectively in yeast by artificially targeting them to pathway-specific complexes. Moreover, the authors show that unique properties of the effectors generate new pathway behaviors: OspF, which irreversibly inactivates mitogen-activated protein kinases, was used to construct a synthetic feedback circuit that shows novel frequency-dependent input filtering. Finally, they show that effectors can be used in T cells, either as feedback modulators to tune the T cell response amplitude precisely, or as an inducible pause switch that can temporarily disable T cell activation. These studies demonstrate how pathogens could provide a rich toolkit of parts to engineer cells for therapeutic or biotechnological applications.

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