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Case Report

Eosinophilic Granulomatosis With Polyangiitis. Review and Case Report of a Patient With Eosinophilia, Lower Limb Mononeuropathy, Sinusitis and Asthma☆

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ABSTRACT

Eosinophilic granulomatosis with polyangiitis is a rare disease frequently associated with asthma and sinusitis. This condition poses a challenge for clinicians because it manifests itself in different phases, as there is often a delay in the diagnosis, with serious consequences for the patients. There are a wide variety of clinical manifestations of the disease such as cutaneous, respiratory, cardiac, ENT, neurological, and renal involvement, to name a few. A case report is presented involving a 26 year old female with a history of chronic rhinosinusitis, vitiligo, and recent onset asthma who was seen in the emergency department a San Jose hospital on many occasions with bronchospasm and eosinophilia. She later developed a peripheral neuropathy in her lower extremity. A literature review on the subject is also presented.

Poliangeítis granulomatosa con eosinofilia. Revisión y reporte de caso de una paciente con eosinofilia, mononeuropatía de miembro inferior, rinosinusitis y asma

Palabras clave:
Vasculitis
Granulomatosis eosinofílica
Churg-Strauss
Neuropatía periférica

RESUMEN

La poliangeítis granulomatosa con eosinofilia es una enfermedad infrecuente, fuertemente asociada al asma y a la sinusitis. Debido a que las manifestaciones de la enfermedad se generan en diferentes fases, el diagnóstico no siempre se realiza de forma oportuna con serias consecuencias para los pacientes. Esta enfermedad presenta manifestaciones cutáneas, respiratorias, cardiacas, otorrinolaringológicas, neurológicas y renales, entre

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Vasculitis ANCA positivas
Poliangeítis

otras. Presentamos el caso de una paciente femenina de 26 años de edad, portadora de una rinosinusitis atópica desde la infancia, vitíligo y asma de inicio reciente, por lo cual consultó en múltiples ocasiones a diferentes servicios de urgencias por broncoespasmos y eosinofilia. Posteriormente desarrolló una neuropatía periférica de la extremidad inferior, que fue valorada en un hospital de la ciudad de San José. Se realizó igualmente una revisión bibliográfica del tema.

Introduction

Eosinophilic granulomatosis with polyangiitis was first described in 1951 by the pathologists Jacob Churg and Lotte Strauss,[1] from the Mount Sinai Hospital in New York City, after the review of 13 cases with similar presentation.

The eponymous "Churg-Strauss Syndrome" was substituted because it was created a single nomenclature for polyangiitis.

It is an infrequent disease; its incidence in the United States is 1-3 cases per 100,000 adults,[2] and its prevalence is of 6.8 cases per million.[3] It tends to affect more men than women, with an average age of onset of 45.5 years, and it is more frequent in people of European descent.[4] For this article it was conducted a review of the bibliographic material published in Costa Rica and it was not possible to find another report of this disease.

It is considered as a vasculitis of small and medium-sized vessels,[5] associated with eosinophilia, necrotizing granulomas and asthma.[5]

In its natural course, the disease has three phases: asthmatic or prodromal, eosinophilic, and vasculitic.[6] Each phase features a variation in the clinical presentation of the picture, which makes difficult the diagnosis. The use of leukotriene inhibitors and anti-IgE[7] has been associated with the onset of the disease.[8,9]

There are diagnostic criteria proposed by the American College of Rheumatology (ACR) (Table 1). The presence of 4 or more criteria provides a sensitivity of 85% and a specificity of 99.7%.[10]

Below we present the case of a female patient with long-standing rhinosinusitis and bronchial asthma who started suffering from a peripheral neuropathy and hypereosinophilia.

Case Presentation

It is a 26 year old female patient, with a history of atopic rhinosinusitis from childhood, vitiligo and asthma of recent onset (one year), who was seen in multiple occasions in different emergency services because of bronchospasm, being designated a therapeutic scheme with inhaled salbutamol, beclomethasone and montelukast.

Table 1 – Criteria of the American College of Rheumatology.[10]

Asthma
Eosinophilia greater than 10%
Mono or polyneuropathy
Pulmonary infiltrates
Abnormalities of paranasal sinuses
Extravascular eosinophilia

Three months prior to the definitive diagnosis, she consulted because a precordial pain, which was cataloged as costochondritis and was managed on an outpatient basis. In the same month she was admitted to a medical center because of a community-acquired pneumonia and a persistent asthmatic crisis. It was performed a blood count, which revealed eosinophilia of 46% with scarce leukocytosis. The eosinophilia the next day was of 67%. The erythrocyte sedimentation rate test reported 51 mm/h. The patient was treated with antibiotics and bronchodilators, and on the fifth day was discharged with scarce wheezing and without breathing difficulty.

Two months before the diagnosis, she was evaluated by the Neurology service due to a left lumbosciatic pain and it was observed an abolition of the left aquilian reflex. At the same time she developed an erythematous pruritic cutaneous lesion, of violaceous appearance, that seemed to be a "bug bite".

She started having paresthesias and muscle spasms in the left foot; a week later she reported pain in the calf of the same limb which prevented her from walking, and for this reason she was admitted to the Service of Internal Medicine of the Hospital Mexico. A MRI scan was performed, which ruled out the presence of a herniated disc. In that same instance it was done a nerve conduction velocity study, which revealed an active acute denervation of the sciatic nerve, common only in the muscles innervated by this nerve below the knee.

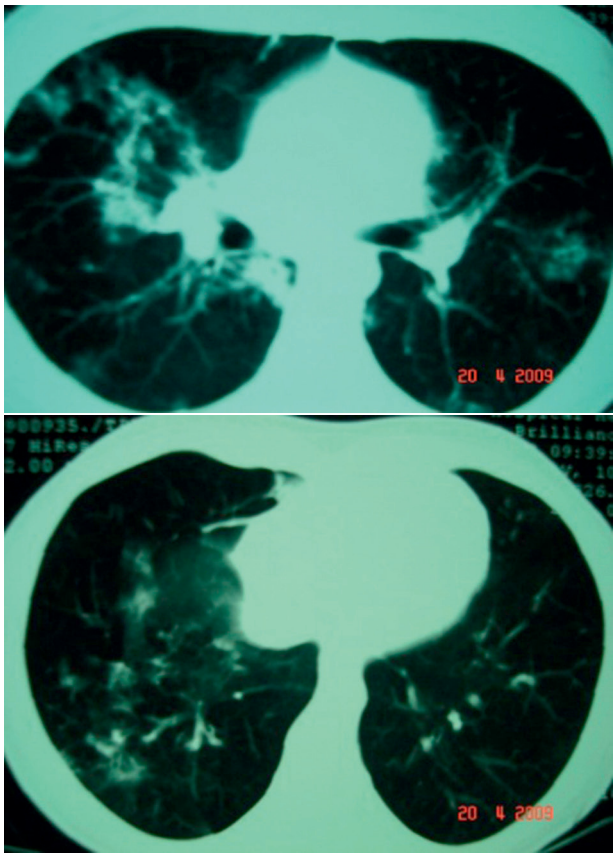
Because of the antecedent of precordial pain it was performed an echocardiogram, which showed a diffuse decrease in cardiac contractility, an ejection fraction of 32-29% and a mild mitral regurgitation.

During this hospitalization, the patient had breathing difficulty, with bronchospasm and hemoptysis, and for this reason it was requested a chest tomography, which showed diffuse parenchymal infiltrates predominantly peripheral, more abundant in the right lung, bronchial thickening and opacities with "ground glass" appearance (Figs. 1 and 2).

A series of laboratory tests was performed, showing the following relevant results:

Normocytic and normochromic anemia, eosinophilia of 55%, increased IL-2 and IL-6, elevated IgE, positive rheumatoid factor, increased interferon alpha and positive p-ANCA (1/40, MPO+).

The patient meets 5 out of the 6 criteria of the ACR, and therefore is diagnosed as an eosinophilic granulomatous vasculitis or Churg-Strauss syndrome.



Figures 1 and 2 – Thoracic tomography at 2 levels with contrast, showing diffuse infiltration of right predominance, bronchial thickening and "ground glass" opacities, taken during the second day of hospitalization.

A treatment with high doses of corticosteroids was started, with a good therapeutic response, generating a normalization of serological markers one month after the beginning of treatment (ESR: 5 mm/h; eosinophils in blood: 3%).

Clinical Manifestations

Pulmonary

The most common manifestation of this pathological entity is bronchial asthma, and it occurs in almost all affected patients. Eosinophilic pneumonitis[11] and alveolar hemorrhage[12] are less frequent manifestations. Since the eosinophilia generates a prothrombotic state, it is also associated with pulmonary thromboembolisms.[13]

Otorhinolaryngological

The most frequent manifestation in this region is chronic sinusitis associated with allergic rhinitis and, in certain cases, nasal polyps.[14] Other less frequent manifestations are: sensorineural deafness, suppurative otitis media, ruptured eardrum,[15] facial paralysis and vertigo.[16]

Cardiac

Cardiac affectation can be manifested in multiple ways, including restrictive or dilated cardiomyopathy, arrhythmias, valvular heart disease, sudden death,[17] pericardial effusion,[18] coronary arteritis[19] and rarely coronary aneurysms.[20]

Musculocutaneous and Articular

Palpable purpura is the most common skin lesion seen in the eosinophilic granulomatosis with polyangiitis.[21] Other cutaneous manifestations include erythematous plaques with or without ulcerations,[22] petechiae,[23] pruritus, subcutaneous nodules and dermatitis.[24] Cutaneous involvement is seen in two-thirds of patients[25] and the extensor surface of the elbow is the most affected location.[26] There are reports of circumscribed[27] and diffuse[28] myositis related with this disease. Synovitis of small and medium sized joints also exists.[29] As an infrequent manifestation we find the necrosis of digits.[30] It seems to exist an infrequent correlation between eosinophilic granulomatosis with polyangiitis and rheumatoid arthritis.[31]

Neurological and Ophthalmological

The most common affectation is a mononeuritis multiplex, which with greater frequency and severity affects the fibular nerves.[32] This condition can progress to a polyneuropathy.[32] The involvement is primarily motor, although it also exhibits sensory disturbances in a lesser percentage and it manifests itself in a similar proportion in the upper and lower limbs.[33] Neurological manifestations tend to be similar, both in distribution and progress, to those of polyarteritis nodosa and rheumatoid arthritis. Neurological manifestations tend to occur later than respiratory.[32] There are also less frequent manifestations such as strokes,[34,35] ischemia of the optic nerve, amaurosis fugax, paralysis of the superior oblique muscle,[36] palsy of the oculomotor nerve[37] and conjunctival affectation.[29]

Renal

Approximately 25% of patients with eosinophilic granulomatosis with polyangiitis have kidney disease.[38] The most frequent histological finding in renal involvement is the necrotizing crescentic glomerulonephritis, although there is a wide variety of inflammatory glomerular conditions.[38] The most frequent clinical manifestation is the rapidly evolving acute renal failure. Microscopic proteinuria and hematuria are present in all patients with renal affectation.[39]

Gastrointestinal

Between 31 and 45% of patients have gastrointestinal manifestations.[40] Abdominal pain is the most frequent symptom,[6] and diarrhea, gastrointestinal bleeding, weight loss, pancreatitis, dehiscence of repaired tissues,[40] intestinal ischemia and hollow viscus perforation[41] are also observed. Acute abdomen occurs infrequently and is associated with a poor prognosis.[42]

Laboratory and Paraclinical Studies

As part of the diagnostic criteria of the ACR we find the presence of eosinophilia higher than 10%, and therefore it is considered as a nonspecific marker of the disease.[43] The concentration of eotaxin-3 is associated with the active phase of the disease and correlates with the elevation of the levels of the acute phase reactants, IgE and the number of eosinophils in peripheral blood.[44]

Between 40[45] and 74.3% of patients diagnosed with this disease are positive for the perinuclear anti-neutrophil cytoplasmic antibody (ANCA), and in a lower percentage, c-ANCA positive.[45] It was found a strong prevalence of ANCA-anti-myeloperoxidase (MPO) versus ANCA-proteinase 3 (PR3),[46] although this trend varies in the case of the populations of the United Kingdom and Northern Europe.[47] ANCA-positive patients show clinical manifestations different from those who lack this marker.[45] The ANCA-negative patients tend to have less renal commitment[24] and a higher incidence of heart disease.[14]

Tissue biopsies have diagnostic significance; in the case of skin biopsies, is recommended to perform them in a period of less than 48 h in case of purpuric lesions and in 72 h in nodular lesions.[21] Extravascular necrotizing granulomas are the most frequent histologic pattern seen in biopsies.[48]

Transient non-segmental consolidations are the most common radiologic findings.[49] The most frequent lesion observed by high-resolution computed tomography is the presence of ground-glass opacities or bilateral diffuse opacities.[50] These manifestations are present in 90% of cases; the presence of septal lines is seen in 50% of cases. Pulmonary abnormalities are seen by tomography in 88% of patients.[51]

In the evaluation of cardiac manifestations, the most frequent electrocardiographic findings are non-specific alterations of the ST segment and T-wave changes. Echocardiography may show left ventricular dysfunction and a small or medium sized pericardial effusion.[25]

Treatment

The traditional treatment to generate a remission in patients with this disease is the use of glucocorticoids or cyclophosphamide.[52,53]

The usual treatment is oral prednisolone at a dose of 1 mg/kg/day for one month, followed by reductions of 2.5 mg per week until reaching 10 mg/day. From this moment is decreased by 1 mg per week until stopping the drug.[54]

Cyclophosphamide is also used to induce remission,[53,54] the drug can be given orally at 2 mg/kg/day for 12 months or in monthly pulses of 0.6 g/m^2.

Cyclophosphamide appears to be especially useful in the reduction of myocardial damage and for the treatment of contractile dysfunction.[55]

It has been seen that the use of methylprednisolone n pulses, added to oral prednisolone at a dose of 1 mg/kg/day, for 3 weeks, is effective for inducing remission.[56]

Table 2 – Five Factor Score 1996.[66]

	Points
Proteinuria > 1 g/24 h	1
Renal insufficiency with creatinine > 1.58 mg/dl	1
Cardiomyopathy	1
Severe gastrointestinal involvement	1
Involvement of the central nervous system	1

The use of rituximab as monotherapy or in conjunction with prednisolone in patients, for 4 weeks, is as effective for the treatment of severe vasculitis as the regime of cyclophosphamide-azathioprine, with a similar number of adverse effects.[57]

In a comparative study it was found that rituximab and azathioprine are very effective drugs in the maintenance treatment of the ANCA-associated vasculitis,[58] although the long-term toxicity of rituximab is not entirely clear yet.

The concomitant use of immunoglobulins and corticosteroids as inductor of remission has proven to be effective.[59] This therapy is also useful in the treatment of residual peripheral neuropathy.[60] It has been also seen that the use of interferon-α,[23] etarnecept and remicade[61] is useful in refractory cases in combination with traditional treatment.

The efficacy of treatment is measured according with the ability to induce remission and to keep the patient free of vasculitis. A patient is considered in remission when 6 months without symptomatology have elapsed,[11] and is considered to be free of disease after 18 months without symptoms upon completion of treatment.[54]

The Birmingham Vasculitis Activity Score is used to determine the presence or absence of active disease in systemic vasculitis.[62] Currently is being used the third version.[63]

Prognosis

Without receiving treatment, up to 50% of patients die within a period of 3 months since the onset of vasculitis.[64]

The leading cause of death in patients with this disease is the associated cardiac involvement.[65]

The Five Factor Score is a scoring system that is used to determine the likelihood of death within a 5 year period in patients with systemic necrotizing vasculitis. It was originally created in 1996.[66] (Table 2). It was reviewed in 2009 (Table 3) and 2 of the 5 previous factors were modified for their use in recently diagnosed patients. In patients with a score of 0, the

Table 3 – Five Factor Score 2009.[67]

	Points
Age > 65 years	1
Renal insufficiency with creatinine > 1.58 mg/dl	1
Cardiomyopathy	1
Severe gastrointestinal involvement	1
Absence of ENT involvement	1

5 year survival is 91%, with 1 point is 79% and with more than 2 points is 60%.[67]

Ethical Disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance to the ethical standards of the responsible committee on human experimentation and according with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors state that patient data do not appear in this article.

Right to privacy and informed consent. The authors state that patient data do not appear in this article.

Conflict of Interest

The authors declare that they have no conflict of interest.

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