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Eosinophilic Granulomatosis with Polyangiitis with ophthalmic involvement: A Case report and Literature Review

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Abstract :
Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a systemic necrotizing vasculitis primarily affecting small blood vessels. It is characterized by extravascular eosinophilic granulomas, peripheral eosinophilia, and often coexists with asthma. This rare condition can affect individuals of any gender and age, presenting with a variety of multisystemic symptoms. Prognosis is largely influenced by cardiac involvement, evaluated using the Five-Factor Score (FFS) to guide treatment decisions. Respiratory manifestations, particularly severe and corticosteroid-dependent asthma, are common in EGPA and may aid in its early diagnosis. In this case report, we describe a patient with an uncontrolled asthma admitted for moderate asthma exacerbation. Clinical examination revealed ocular redness and skin lesions, along with hypereosinophilia on assessment and reticulo-micronodular infiltrates on chest CT scan. EGPA diagnosis was confirmed based on the ACR 1990 criteria, wich have been updated and substituted with more objective criteria in 2022. According to the FFS score, the patient underwent systemic corticosteroid therapy in conjunction with azathioprine, leading to an overall favorable outcome over a 3-year follow-up period.

Introduction :
Eosinophilic granulomatosis with polyangiitis, also known as Churg-Strauss syndrome, is a rare yet severe condition, with potentially life-threatening implications, particularly due to cardiac involvement. It also poses risks to functional outcomes, notably through neurological sequelae and respiratory impairment if not promptly treated. First described in 1951 by Jacob Churg and Lotte Strauss, it falls within the spectrum of ANCA-associated vasculitis, primarily affecting small blood vessels, and is characterized by late-onset asthma or unexplained exacerbations. The clinical presentation varies widely, and diagnosis relies on multiple criteria. Prognosis has improved with the use of corticosteroids, and ongoing research continues to expand therapeutic options for this condition.(1)

Observation :

The patient, Mr. A.Y, is a 28-year-old male with a medical history of intermittent allergic rhinitis and conjunctivitis, confirmed by a positive skin prick test for dust mites. He presents with uncontrolled asthma, as indicated by an ACT score of 10 out of 25. The onset of his symptoms began six months prior to admission, characterized by progressively worsening dyspnea, along with a spasmodic dry cough and daily chest wheezing, without any history of hemoptysis or bronchial mold. These symptoms have developed in the absence of fever, with the patient's general condition preserved. The general examination reveals a patient in good general condition with the presence of bilateral ocular redness. On admission, he was polypneic with an oxygen saturation of 92%, yet showed no indications of respiratory distress or cyanosis. The urine test strip did not reveal any abnormality.

The clinical examination identified bilateral diffuse expiratory wheezing. Presence of well-defined rounded infiltrated papules, erythematous, non-pruritic, scaly, located bilaterally on the elbows, along the extensor surfaces of the forearms, on the trunk, which the patient has recognized for several weeks. The rest of the physical examination did not reveal any notable findings.

Frontal chest x-ray shows the presence of a diffuse interstitial syndrome marked on the right lung. (Figure 1)

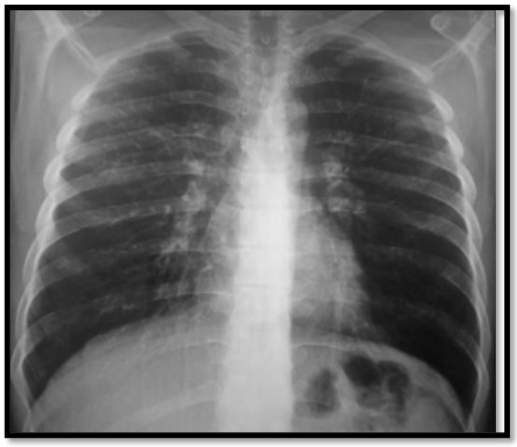


Figure 1: Chest X ray shows a diffuse interstitial syndrome with reticulo-micronodular infiltrates, more pronounced on the right side.

The thoracic CT scan showed infiltrates with scattered nodules and micronodules on the parenchymal window, without a specific distribution (Figure 2). On the mediastinal window, there were no signs of lymphadenopathy or pleuro-pericardial effusion.

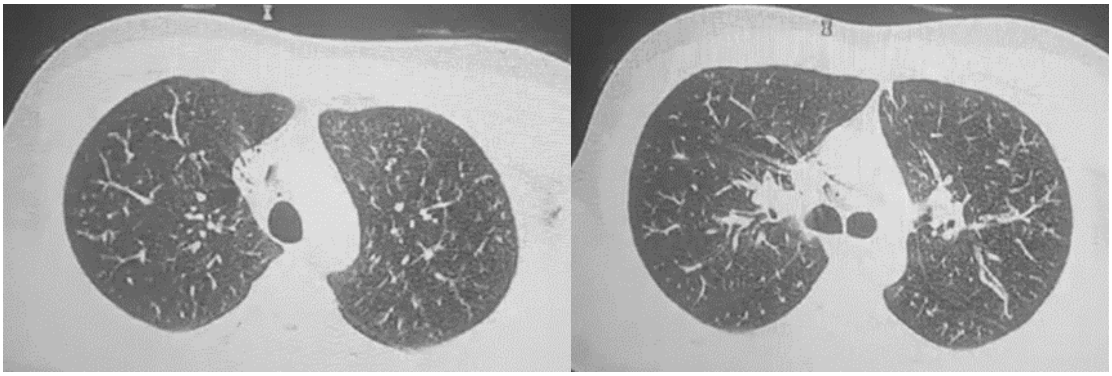


Figure 2: Chest CT scan showing infiltrates on the parenchymal window with scattered nodules and micronodules.

After stabilizing the patient, a laboratory evaluation was performed, indicating hypereosinophilia at 1870/mm³, compared to 1088/mm³ upon admission. Three consecutive negative parasitological stool examinations were conducted, excluding a parasitic etiology for this eosinophilia.

Following cardiac evaluation by an ECG and echocardiography, didn't showed any signs of hypereosinophilic syndrome-related cardiomyopathy.

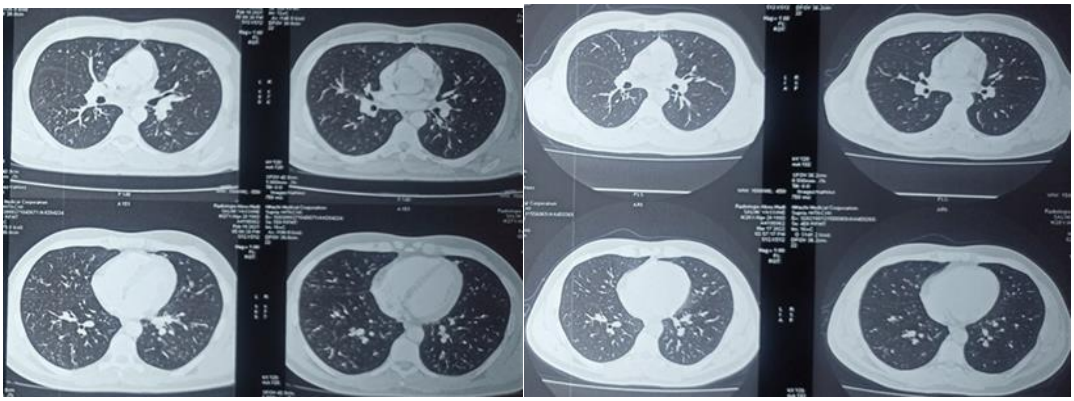
The total IgE levels were elevated, but the specific anti-Aspergillus IgE test returned negative results. So far, the diagnosis of Allergic Bronchopulmonary Aspergillosis seems unlikely. A bronchoalveolar lavage was undertaken, indicating significant alveolar eosinophilia at 54.3%.

Seeking further systemic involvement in the context of eosinophilic granulomatosis, an ENMG was conducted and returned normal. Ophthalmological examination revealed nodular episcleritis. Skin biopsy demonstrated a fibrous dermis with hyper vascularization, with vessels surrounded by a moderate to severe inflammatory infiltrate, characterized by a mix of lymphohistiocytic and polymorphonuclear cells, predominantly eosinophilic, and no evidence of immunoglobulin deposition. In consultation with internists, it is identified as a vasculitis affecting small caliber vessels.

Since this case was hospitalized in 2021, according to the ACR 1990 criteria, our patient meets the criteria for EGPA with a score of 4, which includes asthma, peripheral eosinophilia, pulmonary infiltrates, and vasculitis lesions with eosinophilic infiltrates on biopsy.

The patient's Five-Factor Score (FFS) was 0, prompting the initiation of treatment. This encompassed systemic corticosteroid therapy at a dose of 60 mg/day, supplemented by oral Azathioprine at a dose of 50 mg/day as an immunosuppressant, in conjunction with local corticosteroid therapy (nasal and ophthalmic). Asthma management was adjusted based on staging, and the patient was offered vaccinations against Covid-19, influenza, and pneumococcus to mitigate the risk of serious infections

A significant clinical improvement was noticed, evidenced by an ACT score improving from 10/25 to 25/25, normalization of ambient air saturation to 97%, and resolution of wheezing, skin lesions, and ocular redness. Radiological assessment demonstrated clear improvement on a follow-up chest CT scan conducted monthly (Figure 3).



A B

Figure 3: Parenchymal sections before (A) and after starting EGPA treatment (B)

Reviewing the patient's medical history revealed hypereosinophilia dating back to 2017, coinciding with the onset of recurrent wheezing dyspnea. Initiation of corticosteroid therapy led to marked improvement. Following remission, the internists decided to taper corticosteroids and introduce immunosuppressant therapy at a dose of 150 mg/day. However, upon reaching a dose of 2.5 mg of prednisone and 100 mg of azathioprine, a relapse occurred, characterized by the reappearance of skin lesions, wheezing, and recurrent peripheral neuropathy. Resumption of full doses of corticosteroids and azathioprine resulted in no further relapses.

Presently, the patient is maintained on the minimum effective doses of corticosteroids (7.5 mg/day) and azathioprine (100 mg/day), achieving well-controlled asthma and sustaining complete remission throughout a 3-year follow-up period. (Figure 4)

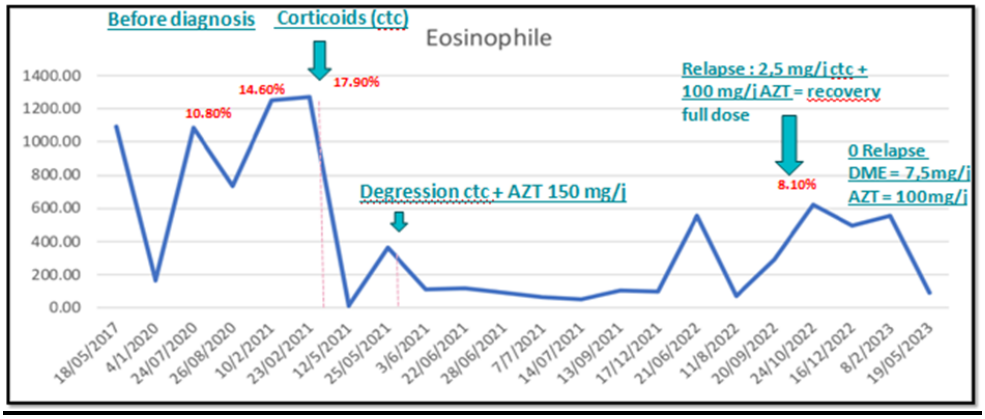


Figure 4: Graph illustrating the temporal variation of eosinophil levels based on the phase of therapeutic intervention in EGPA

Discussion :

Eosinophilic granulomatosis with polyangiitis, previously known as Churg-Strauss syndrome, is a necrotizing vasculitis affecting small blood vessels, often associated with the presence of Antineutrophil Cytoplasmic Antibodies (ANCA) in 40% of cases. It typically occurs in individuals with asthma and is characterized by severe asthma, hypereosinophilia, extrapulmonary manifestations, and predominantly peripheral neuropathy. Cardiac involvement, although uncommon, significantly influences prognosis and accounts for the majority of fatalities (2).

The incidence of eosinophilic granulomatosis with polyangiitis is higher in Great Britain (3), reaching 2.4 cases per million inhabitants. In Spain and France, the incidence does not exceed 0.9 cases per million inhabitants (4). It affects both sexes and can occur at any age, with the highest incidence observed between 30 and 50 years old(5). However, the disease tends to be more severe when it occurs in children and adolescents due to the predominance of cardiopulmonary manifestations(6).

The damage caused by EGPA is multisystemic and polymorphic. The most common manifestations involve the upper respiratory tract, including the nose and sinuses, as well as peripheral nervous system involvement. Cardiac and cutaneous manifestations are also frequently observed. Gastrointestinal and renal symptoms are less common but can be severe.

Patients without ANCA are more likely to exhibit manifestations associated with eosinophilic infiltration, such as cardiac and pulmonary involvement, particularly infiltrates, as observed in our patient's case, or eosinophilic pleurisy. Conversely, one-third of patients with ANCA are more likely to present manifestations directly related to vasculitis, including glomerulonephritis, alveolar hemorrhage, neurological impairment, and purpura.

For the pulmonologist, asthma takes precedence, often presenting as severe and corticosteroid-dependent, yet seldom resulting in mortality. Alveolar hemorrhage, while infrequent, represents a diagnostic urgency. Pleurisy is also uncommon, it might be unilateral or bilateral eosinophilic exudates.

Subsequent to the identification of peripheral and tissue hypereosinophilia, the immunological evaluation, encompassing serum ANCA of the perinuclear type with myeloperoxidase specificity in ELISA, aids in diagnosis when detected. However, the absence of ANCA does not preclude diagnosis. Furthermore, ANCA titers do not correlate with disease progression(6) .

A recent study has indicated the presence of ANCA in the sputum of patients diagnosed with EGPA, even in cases where serum ANCA was negative. However, the potential of sputum ANCA detection as a diagnostic

tool for EGPA remains uncertain and is currently under investigation as a promising avenue of research in the medical field (7).

Sinus scans are conducted when warning signs suggestive of sinusitis or nasal polyps are present. In contrast, cardiac evaluation is routinely performed due to the severity of cardiac involvement in EGPA, which can sometimes be asymptomatic and therefore undetected until irreversible lesions develop without treatment. Cardiac evaluation typically includes an electrocardiogram (EKG) to detect signs of ischemia and echocardiography to assess for endomyocardial fibrosis primarily (8).

Consensual diagnostic criteria for EGPA are currently lacking. Several classification systems have been proposed, including the ACR classification criteria, which were updated in 2022, replacing those from 1990. In the updated criteria, the asthma criterion has been replaced by a more objective criterion based on Respiratory Functional Explorations. The presence of ANCA is now considered a diagnostic criterion, whereas pulmonary infiltrates are no longer included. According to the ACR 1990 criteria, our patient's score is 4, which meets the threshold for EGPA diagnosis. However, under the ACR 2022 criteria, the patient's score is 10, which exceeds the threshold of 6 for EGPA diagnosis.

Once the diagnosis is established, it's crucial to assess the severity of the disease to avoid overtreating. This is achieved using the Five Factors Score, which considers factors such as advanced age, cardiac, renal, and digestive involvement, as well as the absence of orthorhinological damage. Each element corresponds to a point, and treatment is adapted based on the total score. The primary goal of therapy is to achieve early remission and maintain it, while also being vigilant in detecting relapses promptly. It's important to differentiate between relapses of vasculitis and exacerbations of asthma and/or sinusitis, which may be accompanied by an increase in eosinophils but do not necessarily indicate a vasculitis relapse. Adjustments in treatment may be justified in such cases.

Regarding asthma, the aim is to achieve better control of respiratory symptoms without compromising respiratory function, as assessed by Respiratory Functional Explorations.

Achieving this goal primarily involves ensuring good therapeutic compliance, particularly since EGPA typically necessitates chronic treatment. The mainstay of treatment often involves corticosteroids or other conventional immunosuppressants, with biologic therapies being considered in select cases. However, interventions such as plasmapheresis, immunotherapy, and interferon are generally reserved for severe manifestations of vasculitis and have limited indications.

Anti-IL5 drugs have marketing authorization for hypereosinophilic asthma, particularly in refractory cases or recurrences, where they have demonstrated greater efficacy in improving respiratory symptoms compared to placebo. However, their effect on vascular manifestations is less clear. While long-term data is lacking, these drugs are authorized for EGPA by the FDA and the EMA. Anti-IL13 and IL4 therapies have shown effectiveness in controlling hypereosinophilic asthma and orthorhinological manifestations, making them promising candidates for evaluation in EGPA treatment. Anti-IgE therapies are beneficial in severe allergic asthma but do not appear to be effective for EGPA treatment. Anti-CDs are used in refractory and recurrent ANCA vasculitis cases, but their use in EGPA is limited, and some studies have not demonstrated their superiority over conventional immunosuppressants in induction therapy. For example, the study by Reovas, currently pending publication, did not show their benefit. (9, 10,11)

Remission is typically rapid with treatment, achieving rates exceeding 80%. However, relapses are commonly observed, particularly within the first year, and are often associated with ANCA-positive forms of the disease. Overall survival rates exceed 95%, with better outcomes observed in the absence of poor prognostic factors. The risk of mortality is highest during the first year of treatment, primarily attributed to cardiac damage.

In EGPA, pulmonary manifestations typically precede vasculitis in nearly all cases, with asthma onset occurring around age 30. This severe, corticosteroid-dependent asthma often progresses rapidly before extrapulmonary symptoms emerge. It's frequently associated with orthorhinological damage, including rhinitis and nasal polyposis. Alveolar hemorrhages, related to pulmonary capillaritis, are common. Imaging studies may reveal alveolar infiltrates and occasionally unexcavated nodules.

Conclusion :

EGPA, a rare systemic disease, carries life-threatening risks and is characterized primarily by asthma, hypereosinophilia, and vasculitis with granuloma formation. Diagnosis currently relies on the ACR 2022 criteria in front of vasculitis. Treatment strategies, guided by the FFS prognosis score, prioritize corticosteroids which demonstrate high efficacy, with immunosuppressants reserved for severe presentations. Cardiomyopathy remains the predominant cause of mortality in EGPA.

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