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Case Report

Eosinophilic Granulomatosis with Polyangiitis in a 4-Year-Old Child: Is Montelukast and/or Clarithromycin a Trigger?

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Abstract

The aim of the presentation of this case is to discuss whether there is an association with eosinophilic granulomatosis with polyangiitis (EGPA) and the use of montelukast, and clarithromycin and to discuss a successful treatment course. A 4-year-old girl with a preceding history of asthma attacks and increased eosinophil counts was admitted. She had been using clarithromycin for five days and montelucast for a month. She was eventually diagnosed with EGPA with detailed examination. Clinicians should remember EGPA in children with asthma and hypereosinophilia. Patients receiving leukotriene receptor antagonists and/or macrolides should be monitored for developing a multisystem disease. Treatment with immunosuppressive agents may be required to ensure a good prognosis.

Keywords: Children, Churg strauss syndrome (CSS), Clarithromycin, Eosinophilic granulomatosis with polyangiitis, Montelukast

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg Strauss syndrome, CSS) is a rare but potentially life-threatening systemic necrotizing vasculitides predominantly affecting small vessels. It has been rarely reported in children especially before school age.[1-3] The optimal treatment of EGPA may be challenging in pediatric patients.[1] Here we report a 4-year-old girl with recurrent asthma attacks and eosinophilia who was diagnosed with anti-neutrophil cytoplasmic autoantibody (ANCA)-negative EGPA; (i) to remind EGPA in children with asthma and prominent blood eosinophilia; (ii) to discuss if there is an association between the onset of EGPA and the use of leukotriene antagonist-montelukast and macrolide antibiotic clarithromycin; and (iii) to discuss the treatment course for enlightening specialists regarding future pediatric patients presenting with EGPA.

Case Report

A 4-year-old girl was admitted to our hospital with fever and cough. She had a history of asthma and started inhaled fluticasone for 5 months prior to admission; montelukast for 1 month prior and clarithromycin for 5 days prior to admission. Physical examination revealed temperature at 37.7°C, pulse rate of 90/min, blood pressure at 90/55 mm Hg, respiratory rate of 30/min and O_2 saturation of 92% (room air). Lung auscultation revealed prolonged expiration, rhonchi, inspiratory crackles, and intercostal retraction. On laboratory examination; white blood cell count was 13 500/mm^3 with 3780/mm^3 eosinophils, hemoglobin was 12.8 g/dL, and platelet count was 288 000/mm^3. C-reactive protein was 29 mg/L. The blood chemistry was normal. Chest radiograph showed perihilar, peribronchial infitration. Inhaled salbutamol and fluticasone, oxygen, and parenteral ampicillin sulbactam treatment were begun. The most common causes of peripheral blood eosinophilia are; atopic/allergic, infectious (particularly parasitic), hematologic/neoplastic, immunologic, and vasculitic diseases. Work-up included stool studies for ova and parasites on 3 consecutive days, serological parasite infection studies (toxocariasis, trichinellosis, ascariasis, fascioliasis echinococcosis), serum specific IgE levels for a variety of foods/aeroallergens, skin-prick tests were performed. These test results were all normal. On the fourth hospitalization day, necrotic maculopapular rash appeared on the soles of the feet. Test for infectious diseases causing rash, coagulation tests, IgG, IgA , IgM, C3, C4, rheumatoid factor, anticardiolipins, anti-double stranded DNA (anti-Ds DNA), anti nuclear antibody (ANA), anti-smooth muscle antibody, antiphospholipid antibody, P-ANCA c-ANCA, bilateral lower extremity arterial-venous Doppler ultrasonography,

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echocardiography were all normal. Peripheral eosinophil count increased to 38% and serum Ig E level increased to 2860 IU/mL (0-60 IU/mL). Bone marrow examination revealed increase in eosinophil count. Pathological examination of the skin lesion was consistent with eosinophilic vasculitis (Figure 1). Occipitomental or Waters' view radiograph revealed left maxillary sinusitis. The chest HRCT scan showed bilateral peribronchial infiltrates with ground- glass opacification and bronchial wall thickening.

Asthma, eosinophilia, eosinophilic vasculitis, with lung and paranasal sinus symptoms confirmed the diagnosis of EGPA. Inhaled fluticasone (500 µg/d) and methylprednisolone (15 mg/m²/d intravenous route) were started. The findings were improved on the third day of treatment. After 3 days of methylprednisolone treatment, prednisolone was started at a dose of 2 mg/kg/d. On the seventh day of treatment chest radiograph showed significant improvement and eosinophilia decreased to 2%. The patient was followed by pediatric rheumatology and pediatric allergy departments for a year. During follow-up, in attempts to reduce steroid dose to 10 mg/d, respiratory signs and symptoms reappeared. So prednisolone was continued at a dose of 15 mg/d. In this situation, cushing syndrome and dyslipidemia were developed. Due to these complications, azathioprine was initiated at a dose of 1 mg/kg/d orally. Prednisolon was tapered to 10 mg/d after 20 days of azathioprine treatment. She has been using azathioprine for 10 months with a dramatic remission and without myelosuppression.

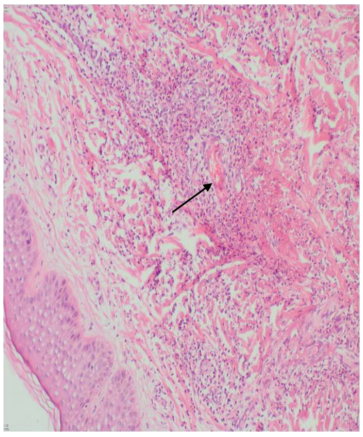

Figure 1. Eosinophilic Vasculitis on Skin Biopsy. The walls of dermal vessels are surrounded densely by lymphocytic and eosinophilic infiltrates. Arrow indicates fibrin which demonstrates blood vessel damage.

Discussion

In 1990, the American College of Rheumatology (ACR) proposed 6 criteria for the diagnosis of EGPA. These are; asthma, blood eosinophilia (>10%), neuropathy, transient lung infiltrates, paranasal sinus abnormalities, and extravascular eosinophils on biopsy. The presence of four or more of criteria yields a diagnosis of EGPA with high sensitivity (85%) and specificity (99.7%).[4] Our patient met the diagnosis of EGPA because of having 5 of the 6 ACR criteria (asthma, eosinophilia greater than 10% on differential WBC count, pulmonary infiltrates, sinusitis and eosinophilic vasculitis on skin biopsy). Maxillary sinusitis appears to be more incidental as there were no polyps, pansinusitis, and necrotizing disease.

EGPA typically develops in three phases: the allergic or prodromal phase, the eosinophilic phase in the second and third decade and the vasculitic phase in the third and fourth decades of life.[5,6] These phases partially overlap and do not appear in a defined order although asthma and chronic rhinosinusitis rarely arise after vasculitic manifestations. Our patient was in the vasculitic phase when she was 4 years old.

EGPA has been included in the spectrum of ANCA-associated vasculitis (AAV) but serum ANCA positivity was relatively low (25%) in children with EGPA.[2] ANCA was also negative in our patient.

The exact etiology of EGPA is unknown. It has been proven that it is associated with *HLA-DRB1*04* and **07* and with *HLA-DRB4*. This suggests a strong $CD4^+$ T lymphocyte activation, possibly triggered by allergens, antigens, infections, and vaccinations.[5] Drugs may also have a pathogenic role. Several reports have described the onset of EGPA in patients receiving leukotriene receptor antagonists (LTRAs) and macrolide antibiotics.[6-10] Bibby et al[7] studied the association between LTRAs and EGPA in cases detected in the FDA Adverse Event Reporting System database. They concluded that LTRA therapy was a suspected cause of EGPA confirmed in 114 cases. The possible role of LTRA therapy in the pathogenesis of CSS is still uncertain. Different hypotheses have been proposed: (i) They may have a direct pathogenic role or may cause idiosyncratic allergic reactions, (ii) It has been postulated that LRAs block the effects of cysteinyl leukotrienes but not the effects of leukotriene B4 which is a chemoattractant for eosinophils, and/or (iii) The association between these drugs and EGPA, may simply be a coincidence.[7,8] Our patient was using both montelukast and clarithromycin which could trigger EGPA attack although it remains speculative.

Hübner et al[9] reported a case suspected to be macrolide-induced CSS. Kränke and Aberer[10] discussed that it could have been induced by macrolide preparations containing tryptophan although some unidentified contaminants might be relevant. Our patient had used both montelukast and clarithromycin. Since both classes of drugs could have been associated with EGPA, we were unable to identify a single cause possibly linked to the induction of the vasculitic reaction.

The primary therapy for EGPA is systemic glucocorticoid. An immunsuppressive agent may be added in patients with advanced or refractory disease and in patients whose disease flares with tapering of systemic

glucocorticoids.[5] Azathioprine, cyclophosphamide, methotrexate, leflunomide, inhaled glucocorticoids, mycophenolate mofetil, intravenous immune globulin, rituximab, interferon-alpha, anti-IgE and anti-IL-5 antibodies can be used as immunsuppressive drugs. We used inhaled and systemic glucocorticoids in our patient. But we reduced the systemic glucocorticoid dose due to occurrence of side effects and azathioprine was started. She has been using azathioprine for 10 months with a dramatic clinical remission.

In conclusion, the low prevalence of EGPA in childhood and the successful treatment course make this case of interest. Similar course was reported in the literature following administration of macrolide antibiotics and LRAs, however, further reports are needed to draw a certain conclusion. To report the successful treatment course of our patient may enhance treatment of future pediatric cases. Clinicians should be reminded of EGPA in pediatric patients with asthma/allergy, worsening respiratory symptoms, rash and abnormal eosinophil counts. Asthmatic patients receiving LTRAs/macrolides should be monitored for the appearance of a multisystem disease. Treatment with immunosuppressive agents may be required for good prognosis.

Authors' Contribution

Authors all participated in drafting the article and revised it critically for important intellectual content. All of them gave final approval of the version to be submitted and the revised version.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The guidelines of the Declaration of Helsinki on medical protocol and ethics were followed in this study. Informed consent was obtained from the parents for publication.

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