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【 CASE REPORT 】

A Pediatric Case of Relapsing Eosinophilic Granulomatosis with Polyangiitis Successfully Treated with Mepolizumab

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Abstract:

We herein report the first pediatric case (a 13-year-old girl) of relapsing eosinophilic granulomatosis with polyangiitis (EGPA) successfully treated with mepolizumab (anti-interleukin-5). She was classified as having EGPA based on the presence of asthma, eosinophilia, pulmonary infiltrates, and extravascular eosinophil infiltration confirmed by a biopsy. She achieved remission after initial oral prednisolone (PSL) therapy, but EGPA relapsed during PSL tapering. Subsequent combined therapy with PSL and tacrolimus did not improve the recurrent disease. Intravenous methylprednisolone pulse therapy was started, followed by oral PSL. During PSL tapering, mepolizumab was added to the treatment, which resulted in sustained remission and successful PSL tapering.

Key words: eosinophilic granulomatosis with polyangiitis, mepolizumab, pediatric case, relapsing case

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), known as Churg-Strauss syndrome (CSS) until 2012 (1-3), has been included in the spectrum of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (4). Around 40% of EGPA patients are positive for serum ANCAs (2). In 1990, the American College of Rheumatology (ACR) clarified the classification criteria for CSS: namely, asthma, eosinophilia >10% on different white blood cell counts, mono- or polyneuropathy, non-fixed pulmonary infiltrates on radiographs, paranasal sinus abnormality, and extravascular eosinophils confirmed by a biopsy. The presence of ≥4 of these 6 criteria yielded a sensitivity of 85% and a specificity of 99.7% (3).

Although the pathophysiology of EGPA has not been fully confirmed, both Th2 and Th1/Th17 immune responses are considered to be involved in its pathogenesis (2). Of the associated cytokines in these immune responses, interleukin (IL)-4, IL-5, IL-13, and IL-17 are known to be related to EGPA (2, 5). Among them, IL-5 is an essential cytokine for the eosinophil maturation, activation, and survival (5).

EGPA management relies on pharmacological agents chosen according to disease severity (6, 7). Corticosteroids are often used first, but relapses are frequent. Immunosuppressants are required for patients with recurrent disease (6, 7). Currently, eosinophil- and B cell-targeted therapies have been increasingly frequently applied to treat EGPA. These biologicals include omalizumab (a humanized anti-IgE monoclonal antibody), mepolizumab (a humanized anti-IL-5 humanized monoclonal antibody), and rituximab (a mouse-human chimeric anti-CD20 monoclonal antibody) (6, 7). Among them, mepolizumab is the first biological approved to treat EGPA (7).

EGPA is uncommon in childhood (8-10). In a nationwide Japanese cohort, the mean age of EGPA patients was 58 years old (11). Previous large case series of pediatric EGPA in the United States, the Kingdom, and France reported 9, 13, and 14 cases, respectively (8-10). These studies highlighted clinical differences between pediatric and adult EGPA patients. In pediatric EGPA, eosinophilia, in combination with upper respiratory, pulmonary, musculoskeletal, neurologic, cardiac, gastrointestinal, and cutaneous manifes-

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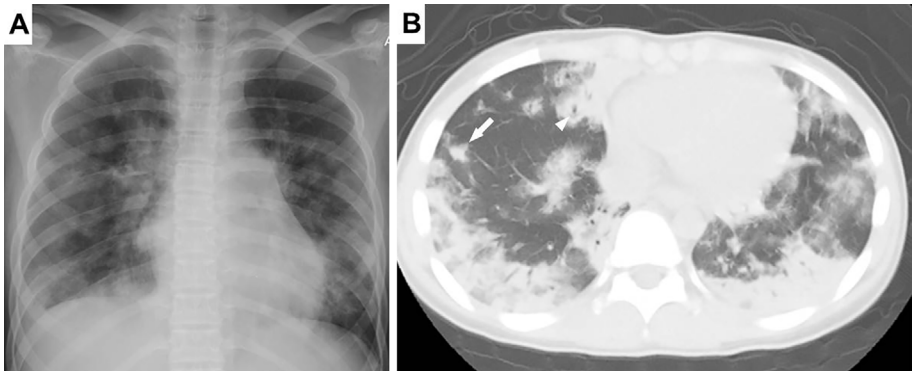

Figure 1. **Chest X-ray and computed tomography on admission. (A) Chest X-ray shows bilateral reticular shadows. (B) Computed tomography reveals non-segmental bilateral consolidation with peripheral distribution, small nodules (arrow), and bronchial wall thickening in the bilateral lungs (arrowheads).**

tations is frequently observed (8). Pediatric EGPA is a potentially life-threatening vasculitis (9). Systemic symptoms develop earlier than in adult patients, mainly during the eosinophilic phase (10). Corticosteroids are the mainstay initial therapy for pediatric EGPA patients, but steroid-related side effects regularly occur (8-10). Recently, targeted therapies using omalizumab and rituximab have been successfully used to treat pediatric patients with refractory EGPA (12, 13).

We herein report the first case of a pediatric patient with relapsing EGPA successfully treated with mepolizumab.

Case Report

A 13-year-old Japanese girl with an 8-month history of asthma presented with a fever, cough, abdominal pain, diarrhea, weight loss (6 kg/month), and eosinophilia (23,894 eosinophils/μL). She was treated with intravenous infusion antibiotics and oral prednisolone (PSL) (30 mg/day) at a local hospital. Thereafter, her symptoms improved. However, during PSL tapering, she suffered from a high fever, cough, abdominal pain, myalgia, and bilateral leg pain. She was then referred to our hospital.

On admission, her height was 153.3 cm, weight 41.4 kg, and body temperature 38.8℃. A physical examination revealed epigastric tenderness. A urinalysis showed no proteinuria or hematuria. Her white blood cell count was 13,700/μL with 30.0% eosinophils, hemoglobin 13.8 g/dL, and a platelet count of 388,000/μL. Serum total protein was 7.0 g/dL, aspartate transferase 20 U/L, alanine transferase 14 U/L, lactate dehydrogenase 301 U/L, blood urea nitrogen 10.0 mg/dL, and creatinine 2.3 mg/dL. Serum C-reactive protein was 10.56 mg/dL, IgG 1,183 mg/dL, IgA 278 mg/dL, IgM 120 mg/dL, IgE 1,471 IU/mL, C3 162 mg/dL, C4 58 mg/dL, and CH_{50} 59 U/mL. Antinuclear antibodies, myeloperoxidase-ANCA, and proteinase 3-ANCA were negative. Blood and urine cultures were negative.

Bone marrow aspiration showed hypercellular bone marrow with a marked increase in eosinophils without dysplasia. FIP1L1-PDGFRA gene rearrangement was not detected by fluorescence *in situ* hybridization.

Chest X-ray showed bilateral reticular shadows (Fig. 1A). Systemic computed tomography revealed non-segmental bilateral consolidation with peripheral distribution, small nodules, bronchial wall thickening in the bilateral lungs (Fig. 1B), and splenomegaly. Bronchoalveolar lavage fluid contained many eosinophils (144,300 cells/mL). Lung biopsy specimens showed small nodular lesions with eosinophilic infiltration. A cardiac ultrasound examination showed no abnormal findings. Upper gastrointestinal endoscopy showed no abnormal findings, but lower gastrointestinal endoscopy revealed multiple areas of mucosal redness and ulcer scars from the ileum to the rectum. Colon biopsy specimens showed slight eosinophilic infiltration in the submucosa.

Based on the ACR classification criteria (3), she was classified as having EGPA: the presence of asthma, eosinophilia >10% on different white blood cell counts, non-fixed pulmonary infiltrates on radiographs, and extravascular eosinophil infiltration on biopsy findings.

Fig. 2 shows the clinical course. She was treated with 50 mg/day (1.2 mg/kg/day) of oral PSL, and her condition subsequently improved. She was discharged after PSL tapering. During PSL tapering to 10 mg/day, she again suffered from cough, and eosinophilia recurred. The dosage of PSL was increased to 20 mg/day. The patient and her family did not want to use immunosuppressants with possible infertility side effects (e.g., cyclophosphamide). After a discussion with the patient and her mother, combined therapy with 20 mg/day of PSL and tacrolimus was started. This drug was selected in light of the large amount of published data showing no evidence of any increase in malformations in pregnant women exposed to tacrolimus (14). Nine days after combined therapy, the dosage of tacrolimus was increased from 1 mg/day to 2 mg/day because the trough blood level of the drug was 1.3 ng/mL. However, remission was not achieved. In addition, bilateral leg pain and a small toe ulcer appeared.

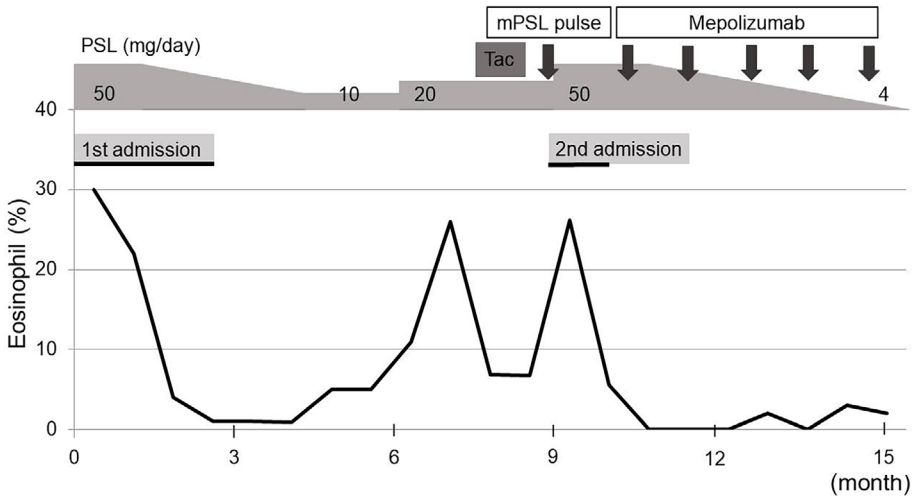

Figure 2. **Clinical course. mPSL: methylprednisolone, PSL: prednisolone, Tac: tacrolimus**

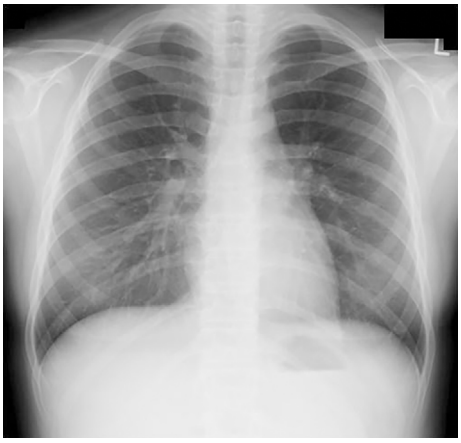

Figure 3. **Chest X-ray after one month of mepolizumab treatment. A significant improvement in the pulmonary radiological findings is observed.**

She was readmitted to our hospital. After intravenous methylprednisolone (mPSL) pulse therapy (500 mg/day for three days) followed by 50 mg/day of oral PSL, her symptoms and eosinophilia improved, and she was discharged. During PSL tapering, therapy with mepolizumab (300 mg administrated subcutaneously every 4 weeks) was started with consent from the patient and her mother. Based on the DREAM study findings in patients with severe asthma over 12 years of age (15), the potential risks and benefits of the proposed therapy (safety and effects for steroid-sparing and recurrence prevention) were discussed. A significant improvement was seen in the clinical symptoms (respiratory, musculoskeletal, and cutaneous symptoms), eosinophilia, and pulmonary radiological findings after one month of mepolizumab therapy (Fig. 2, 3). Sustained disease remission was achieved even after reducing the dose of PSL to 4 mg/day during continued mepolizumab therapy.

Discussion

EGPA is a rare disease that usually manifests in adulthood with an estimated incidence of approximately 0.1 to 2.7 new cases per 1 million people per year (2). According to the review of Fina et al. (10) in 2018, only 38 articles describing pediatric cases of EGPA are listed in the PubMed database, with 92 cases cited (mostly individual case reports). In pediatric patients with EGPA, eosinophilia with respiratory involvement is frequently observed, and ANCA titers are often negative (8-10), as in our patient. As shown in the previous studies of pediatric patients with EGPA (8-10), our patient had various clinical manifestations caused by gastrointestinal, musculoskeletal, and cutaneous involvement. Lung and colon biopsy findings were not contradictory to those observed in EGPA (3).

EGPA therapy is based on corticosteroids (6, 7). In severe and refractory cases, immunosuppressants including cyclophosphamide are often used (6, 7). In the previously reported series of pediatric EGPA (8-10), the general approach was the induction of remission (high-dose corticosteroids alone or combined with another immunosuppressant), followed by the maintenance of remission therapy (lower-dose of corticosteroids or combined with a maintenance immunosuppressant) or institution of second-line therapy for failed induction. As the second-line therapy, immunosuppressants such as cyclophosphamide, azathioprine, and mycophenolate mofetil have been used (8-10). Steroid-related side effects, such as Cushing's syndrome, osteoporosis, growth delay, and infections, regularly occurred (8-10). In a French cohort study (10), the rate of relapse was significantly higher in pediatric patients (64.3%) than in adult patients (25.3%). Therefore, more specific therapeutic options for EGPA are required to reduce therapy-related adverse events, especially in pediatric patients.

The pathogenesis of EGPA is not well understood, but eosinophils, T cells, and B cells are thought to play impor-

tant roles along with genetic and environmental factors (2, 16). Among these cells, eosinophils are considered to play a prominent role in the clinical manifestations of EGPA (17). The proliferation and maturation of eosinophil progenitors in the bone marrow and the migration and survival of peripheral blood eosinophils are mediated by a number of humoral factors, including IL-5 (17, 18). Indeed, Jakiela et al. (19) observed the increased production of IL-5 in the airways of patients with active EGPA. Therefore, inhibition of IL-5 offers a rational therapeutic approach for managing EGPA patients (6, 7).

Mepolizumab has recently been used as an anti-IL-5 agent to treat severe eosinophilic asthma (20). Furthermore, its use has also been explored in other diseases that share some pathogenic mechanisms with eosinophilic asthma, including GPA (21). In a randomized controlled trial published in 2017 (22), mepolizumab at a dose of 300 mg administered subcutaneously every 4 weeks proved effective in prolonging the period of disease remission, allowing for reduced steroid use. The positive results of this study led to the approval of mepolizumab in adult patients with EGPA by the United States Food and Drug Administration in 2017 (21). Nucala® (mepolizumab) is currently licensed in the United States, Japan, and more than 30 countries worldwide (23). According to a recent systemic review, mepolizumab is efficacious and safe to use in patients with EGPA (24) and it may improve the remission rate, reduce the relapse rate, and allow for reduced steroid use.

Our pediatric EGPA patient achieved remission after high-dose oral PSL therapy, but the disease relapsed during PSL tapering. Combined therapy with middle-dose PSL and tacrolimus was selected for reinduction. However, sustained remission was not achieved after this therapy. Intravenous mPSL pulse therapy was effective for reinduction, and 300 mg mepolizumab administered subcutaneously every 4 weeks safely enabled steroid tapering to 4 mg/day of PSL. The DREAM study showed that mepolizumab (75 mg, 250 mg, or 750 mg administered intravenously every 4 weeks) is a safe and effective treatment in patients with severe asthma over 12 years of age (15). This study also showed that a 250 mg injection, equivalent to a 300 mg subcutaneous injection (25), had similar efficacy to a 750 mg injection. Schwarz et al. (26) recently suggested that mepolizumab could be a new, safe, and effective treatment option for pediatric patients with hypereosinophoic syndrome. They described two cases of severe pediatric hypereosinophoic syndrome successfully treated with mepolizumab (750 mg administered intravenously every 4 to 6 weeks after first-line therapy). In these patients, treatment with systemic corticosteroids was terminated, and no significant intolerance appeared. Based on the clinical course in our patient, 300 mg mepolizumab administered subcutaneously every 4 weeks can be considered as an add-on therapy with a steroid-sparing effect in pediatric cases of relapsing or refractory EGPA.

To our knowledge, this is the first report of a pediatric patient with relapsing EGPA successfully treated with mepolizumab. This anti-IL-5 agent may be a promising therapeutic option in the management of pediatric patients with relapsing or refractory EGPA, sparing the use of high-dose corticosteroids and reducing steroid-related adverse effects.

The authors state that they have no Conflict of Interest (COI).

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