# Successful use of mepolizumab for severe hypereosinophilic vasculitis with c-ANCA positivity in a previously healthy 7-year-old boy

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**An unusual case of a pediatric patient with severe eosinophilic vasculitis causing digital ischemia is reported. The patient responded well to the anti–IL-5 agent mepolizumab, lending support for use of mepolizumab in pediatric patients with hypereosinophilic syndromes. (J Allergy Clin Immunol Global 2023;2:124-6.)**

***Key words:*** *Eosinophilic vasculitis, mepolizumab, eosinophilic granulomatosis with polyangiitis, idiopathic hypereosinophilic syndrome, pediatric case report*

*Abbreviations used*
AEC: Absolute eosinophil count
EGPA: Eosinophilic granulomatosis with polyangiitis
EoV: Eosinophilic vasculitis
GPA: Granulomatosis with polyangiitis
HES: Hypereosinophilic syndrome
I-HES: Idiopathic hypereosinophilic syndrome
PR3: Proteinase 3

Hypereosinophilic syndrome (HES) is a rare disorder characterized by marked peripheral hypereosinophilia (absolute eosinophil count [AEC] > 1.5 k/μL) causing end-organ dysfunction.[1] Eosinophil mediators promote inflammation and thrombosis, resulting in endothelial damage that can be devastating. Pediatric HES is quite uncommon, as most patients are 20 to 50 years of age at the time of diagnosis.[1] Once clonal disorders and more frequent causes of eosinophilia have been excluded, other subtypes of HES should be considered, including eosinophilic granulomatosis with polyangiitis (EGPA) and idiopathic HES (I-HES).

Initial treatment is aimed at lowering peripheral eosinophil counts, which is frequently achievable with corticosteroids. However, not all patients respond to corticosteroids, and prolonged use can lead to significant morbidity. Mepolizumab, a mAb against IL-5, which is a key driver of eosinophilia, represents a promising alternative. Here, we present the case of a pediatric patient with hypereosinophilia and vasculitis leading to digital necrosis who demonstrated excellent clinical response to mepolizumab.

## CASE DESCRIPTION

A 7-year-old male with no significant medical history presented with acute onset of painful digital cyanosis. The results of a review of systems for atopic and respiratory disease, recent illness, or travel, were negative. Examination revealed discoloration of the patient's fingertips, purpuric macules on his feet, and livedoid patches on his toes (Fig 1, *A* and *B*), with normal motor and sensory examination findings. Laboratory tests revealed leukocytosis to 27.4 k/μL, an AEC of 15.7 k/μL, transaminitis (alanine transaminase level, 154 U/L; aspartate transaminase level, 152 U/L), and an elevated erythrocyte sedimentation rate (45 mm per hour). A chest radiograph showed prominent lung markings. Nifedipine and topical nitroglycerin were administered with minimal effect. Because of progression of ischemia, the patient was admitted to the intensive care unit for epoprostenol drip. On hospital day 3, his AEC reached 17 k/μL.

Further laboratory tests revealed an elevated IgE level (2062 IU/mL) and cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) positivity (proteinase 3 [PR3] antibody titer >8). The results of a parasitic workup were negative. An echocardiogram revealed normal function. Computed tomography showed maxillary sinus mucosal thickening, pleural effusions, hilar adenopathy, moderate ascites, periportal lymphadenopathy, and gallbladder hydrops. The results of an ophthalmologic examination were within normal limits. Arterial duplex showed no stenosis. The results of bone marrow biopsy were unremarkable. Skin biopsy revealed thrombotic vasculopathy with superficial and deep perivascular and interstitial dermatitis with eosinophils.

Three days of pulse steroids lowered the patient's AEC to zero, his perfusion improved, and he was transitioned to a steroid taper. On days 2 and 3 of the taper, his AEC reached 0.9 k/μL and 1.8 k/μL, respectively. An additional dose of pulse steroids was given, and his AEC again reached zero. Steroid dependence was suspected, necessitating a steroid-sparing alternative. He subsequently received 100 mg of subcutaneous mepolizumab with

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Informed consent was obtained from the patient's guardian regarding publication of data and images.

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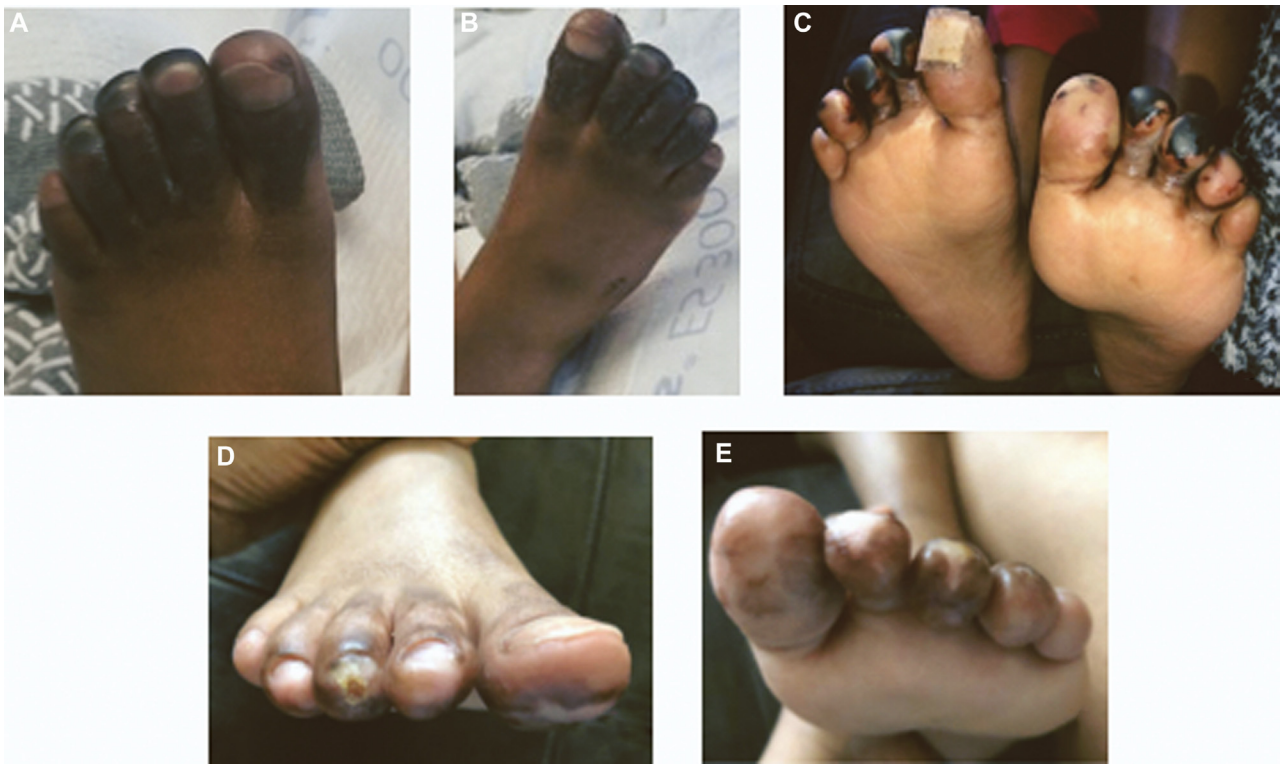


**FIG 1.** Digital skin findings: ischemia (**A** and **B**), necrosis (**C**), and autoamputation and healing (**D** and **E**).

improvement. Epoprostenol was discontinued, and he was discharged with a steroid taper and monthly mepolizumab. No genetic mutations were identified through targeted primary hypereosinophilia panel or whole exome sequencing. The results of testing with an autoimmune lymphoproliferative disorders panel, testing for COVID-19 antibodies, and fluorescence *in situ* hybridization testing for FIP1L1-PDGFRA were negative. Two months after discharge, because of significant granulation that had occurred before mepolizumab initiation, the patient's toes formed eschars (Fig 1, *C*) and autoamputated (Fig 1, *D* and *E*). His eosinophil counts have remained at zero, except for an increase to 0.4 k/μL when mepolizumab spacing to 6 weeks was attempted (Fig 2). He continues to receive mepolizumab every 4 weeks.

## DISCUSSION

EGPA is characterized by asthma, eosinophilia, and vasculitis, with the disease generally progressing in that order.[2] Asthma is present in nearly all patients, although patients without asthma, including children, have been described.[2,3] EGPA, along with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), comprise the ANCA-associated vasculitides. The result of testing for ANCA is positive in 40% to 60% of patients with EGPA, with myeloperoxidase ANCA being most common.[4] Detection of PR3 ANCA, such as in our patient, is rare in EGPA. A cross-sectional, multicenter study found that 50% of patients with EGPA were myeloperoxidase ANCA–positive and just 2.5% were PR3 ANCA–positive.[5]

According to the EGPA guidelines released in March 2022, a score of 6 points or higher yields a sensitivity of 85% and specificity of 99% for diagnosis.[6] Three points each are given for asthma and nasal polyposis, 1 point for mononeuritis multiplex, 5 for an AEC higher than 1 k/μL, 2 for eosinophils on biopsy, minus 3 for PR3 ANCA positivity, and minus 1 for hematuria. Our patient scored 4 points, thus not fulfilling the current criteria. However, these guidelines have been studied only in adults, and we note that although the criteria are excellent at differentiating EGPA from other types of vasculitides (particularly the ANCA-associated vasculitides), they were not developed to differentiate "vasculitis mimics" or "related HESs."[6] This is reflected in the criteria of PR3 ANCA and hematuria, which yield negative points, owing to their greater association with GPA and MPA, respectively.[6] Given our patient's PR3 ANCA positivity, which is highly associated with GPA (occurring in 80% of patients), an overlap EGPA-GPA syndrome could be considered. However, eosinophilia—especially to the degree seen in our patient—is not characteristic of GPA, whereas it is part of the diagnostic criteria of EGPA. Additionally, GPA is associated with kidney dysfunction far more than is EGPA (in 70% vs 25% of cases, respectively), and our patient's kidney function remained intact. Although digital ischemia and necrosis are rare in both GPA and EGPA, EGPA is in general more likely than GPA to feature cutaneous manifestations at presentation (47% vs 34%, respectively).[7]

I-HES is a diagnosis of exclusion when the etiology of eosinophilia remains unknown despite a thorough workup, including for malignancy, drug hypersensitivity, parasitic infection, and EGPA. In contrast to EGPA, I-HES does not classically present with ANCA positivity or vasculitic complications.[4] Lefèvre et al used the term *idiopathic eosinophilic vasculitis* (EoV) to describe a subset of patients with hypereosinophilic vasculitis without asthma, suggesting that this may represent a distinct form of HES characterized by eosinophil-driven vascular damage

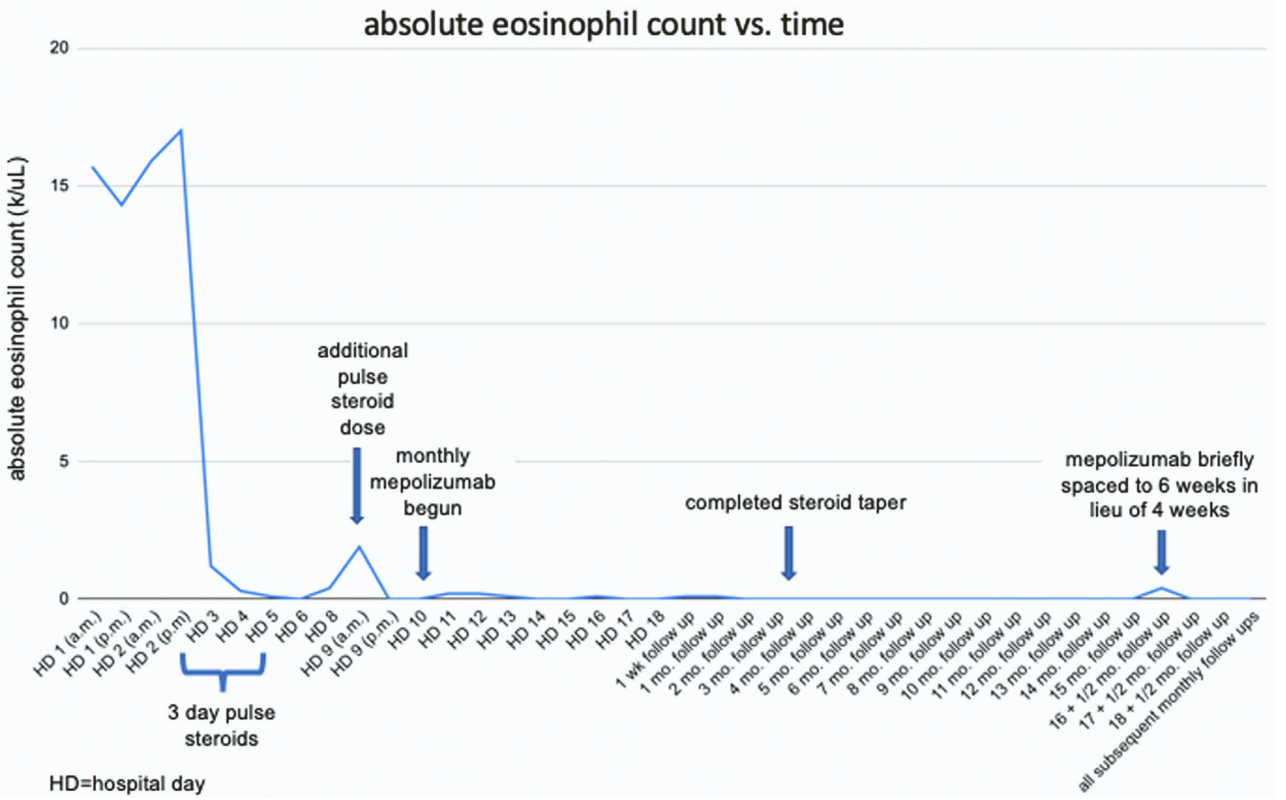


**FIG 2.** Absolute eosinophil count over time.

rather than EGPA in nonasthmatic individuals.[8] However, patients developed hypereosinophilic vasculitis in the absence of asthma *and* ANCA positivity, thus excluding our patient's presentation.

Although our patient's lack of asthma supports a diagnosis of I-HES, his ANCA positivity (albeit PR3 ANCA positivity) and vasculitic complications, are more consistent with EGPA. Given overlapping features, mepolizumab was chosen as a steroid-sparing agent, as it has been shown to effectively treat both conditions, albeit in older patients.[9,10] Per Lefèvre et al, mepolizumab may be used for patients with EoV, given its success in EGPA and I-HES, of which EoV may be a subtype.[8] Mepolizumab is approved for adults with EGPA, children older than 6 years with severe asthma, and patients older than 12 years with HES. Here, we have demonstrated an off-label, though successful, use of mepolizumab.

This is an unusual presentation of hypereosinophilia, severe vasculitis, and digital necrosis in a pediatric patient. We suggest workup for EGPA in pediatric hypereosinophilia, even in the absence of respiratory disease. The paucity of literature on pediatric hypereosinophilic conditions makes their diagnosis and management challenging. Although our patient responded well to mepolizumab, more research regarding its efficacy and safety for hypereosinophilic diseases in young patients is necessary. It is our hope that with further research, more insight will be gained into the diagnosis and treatment of HESs in pediatric populations.

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