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Panuveitis Associated With Idiopathic Hypereosinophilic Syndrome

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Abstract

Purpose: To describe a patient with idiopathic hypereosinophilic syndrome (HES) associated with panuveitis. **Methods**: An interventional case report is presented. **Results:** A 70-year-old woman presented with intermittent cutaneous eruptions, bilateral panuveitis, and a ground-glass pattern on chest CT-scan, with isolated eosinophilia of 12.8×10^9/L. A complete uveitis workup was performed, and the patient was evaluated to rule out secondary causes of eosinophilia, with a thorough focus on infections, eosinophilic granulomatosis with polyangiitis, sarcoidosis, and drug-related syndromes. A bone marrow biopsy ruled out primary eosinophilia. Cytogenetics were also negative. Under steroid treatment there was no recurrence of skin rashes and panuveitis was satisfactorily resolved, but further use of mepolizumab was needed to normalize the hemogram. **Conclusions:** The diagnosis of HES requires a comprehensive evaluation. Ocular involvement is rare. We present the ocular findings during the acute stage for the first time, along with the current management approach.

Keywords

panuveitis, eosinophilia, idiopathic hypereosinophilic syndrome, ocular inflammation, vitritis, retinochoroidal infiltrates

Introduction

Hypereosinophilia (HE) is defined as a peripheral absolute eosinophil count (AEC) greater than 1.5×10^9/L.[1] It is a rare condition, with an age-adjusted incidence estimated to be around 0.4 cases per 1 000 000 population. Depending on the AEC, HE is graded as mild (AEC 0.35-1.5×10^9/L), moderate (AEC 1.5-5×10^9/L), and severe (AEC $> 5 \times 10^9$/L).[2] The World Health Organization (WHO) has classified eosinophilia as being reactive, primary (clonal), or idiopathic. The most frequently damaged organs in the context of HE are the skin, lungs, intestines, and, to a minor extent, cardiac tissue.[1]

Idiopathic hypereosinophilic syndrome (HES) is a diagnosis of exclusion assumed if there is a peripheral AEC $> 1.5 \times 10^9$/L and $\geq$10% of eosinophils, with tissue involvement, after ruling out reactive and primary causes of HE. Conventionally, an AEC $> 1.5 \times 10^9$/L maintained for at least 6 months was necessary as a diagnostic criterion, but recently this requirement has been reduced to as short as 2 to 4 weeks due to advances in diagnostic tools.[1] Ocular inflammation in the context of HES is a very rare finding. Two cases of pediatric uveitis with a poor visual prognosis have been described in the literature.[3,4] We report a patient presenting with HES with bilateral panuveitis and describe the sequential management performed.

Case Report

A 70-year-old woman from Colombia complained of recurrent, generalized, and self-limited skin rashes (Figure 1, A) and visual worsening. She had been successfully treated for Waldenström macroglobulinemia with 6 cycles of bendamustine and rituximab from November 2022 to April 2023. After achieving complete resolution, she underwent hematologic workup due to fluctuant HE. Her chronic medications were fenofibrate, carvedilol, omeprazole, and naproxen as needed. Trimethoprim-sulfamethoxazole, folic acid, and acyclovir were added during the chemotherapy cycles and stopped after resolution of the macroglobulinemia.

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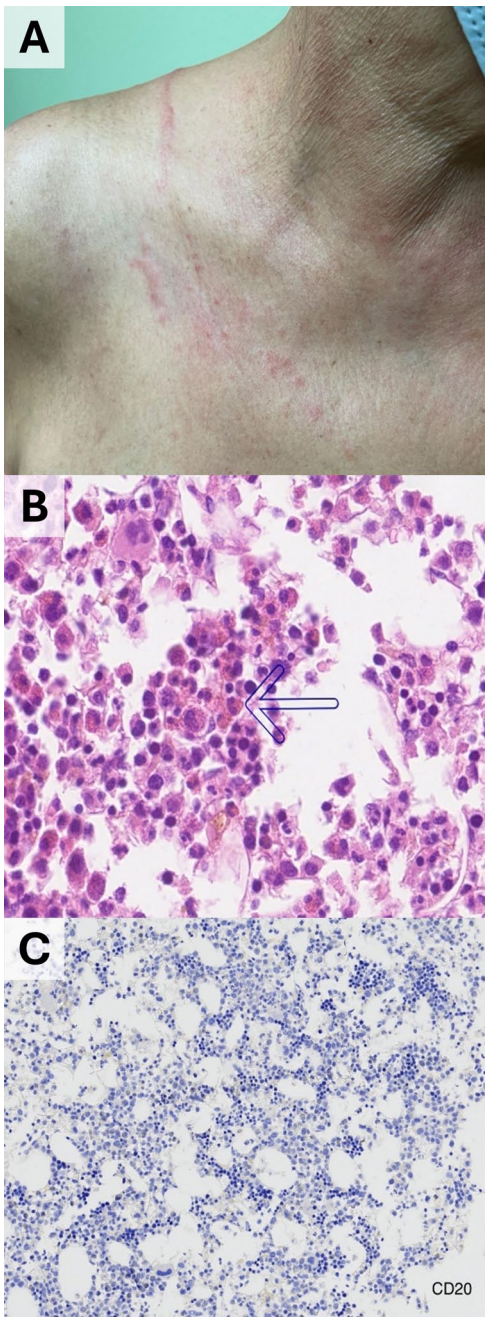

Figure 1. (A) Skin rash. (B) Hematoxylin-eosin–stained section of the bone core biopsy shows hypercellular marrow for the patient's age with eosinophils (blue arrow). (C) CD20 immunostaining of the bone marrow biopsy shows the absence of infiltration by B-cell lymphoma.

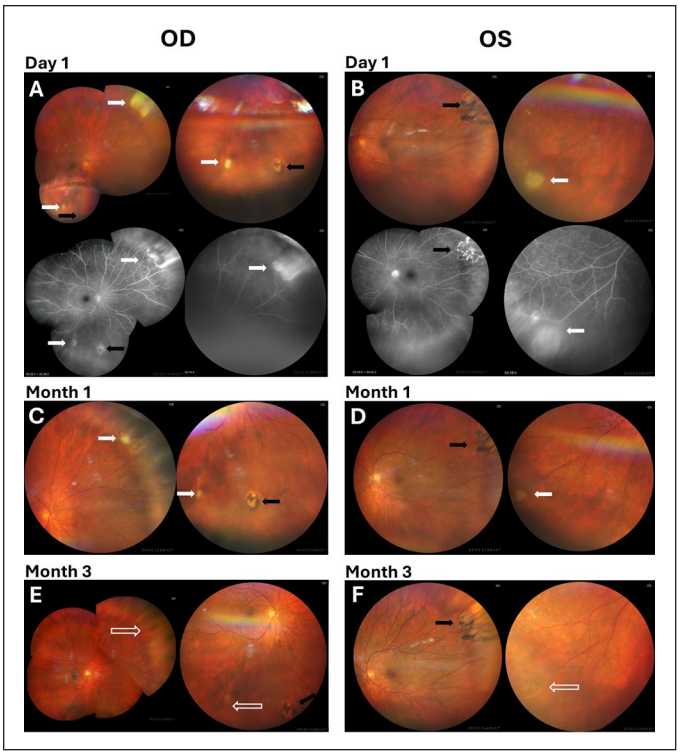

Figure 2. (A) Baseline imaging of the right eye: Wide-field retinography montage (upper left) shows vitritis, 2 acute yellowish retinochoroidal infiltrates (white arrows) and 1 chorioretinal scar (black arrow). The inferior acute infiltrate and chorioretinal scar are magnified in the upper right. Fluorescein angiography montage (lower left) demonstrates hyperfluorescent acute infiltrates (white arrows), and progressive staining of the superotemporal infiltrate (lower right, white arrow). (B) Baseline imaging of the left eye: Wide-field retinography (upper left) shows vitritis, a superotemporal chorioretinal scarring area (black arrow) and an acute inferonasal yellowish retinochoroidal infiltrate located beneath the retinal vessels (white arrow). Fluorescein angiography montage (lower left) demonstrates a scarring area with a mix hyper- and hypofluorescent pattern (black arrow) and hyperfluorescence of the inferonasal acute infiltrate (lower right, white arrow). (C) Right eye imaging after 1 month: Wide-field retinography demonstrates reduction in the size of the superonasal (left, white arrow) and inferior (right, white arrow) infiltrates. The focal chorioretinal scar remains stable (right, black arrow). (D) Left eye imaging at 1 month: Wide-field retinography shows a stable superotemporal chorioretinal scar (left, black arrow) and a reduction in the size of the inferonasal acute infiltrate (right, white arrow). (E) Right eye imaging at month 3: Wide-field retinography demonstrates clear details of the posterior pole, complete regression of the peripheral superonasal infiltrate (left, white hollow arrow), and a healed inferior infiltrate with subtle retinal pigment epithelium pigmentation (right, white hollow arrow). (F) Left eye imaging at month 3: Wide field retinography reveals clear details of the posterior pole, the superotemporal scarring area without changes (left, black arrow), and regression of the inferonasal infiltrate (left, white hollow arrow).

She started complaining about skin rashes in June 2023, and in July 2023 she consulted the ophthalmology emergency department, complaining of bilateral blurry vision and floaters, with a best corrected visual acuity (BCVA) of 20/50 in the right eye (OD) and 20/32 in the left eye (OS). Ocular findings revealed normal intraocular pressure (OD 14/OS 13 mmHg), mild cataracts (NO2 CO2 according to the LOCS III classification) in both eyes (OU), anterior chamber cells OU (1+ according to the SUN grading system), vitritis OU (1+ according to the SUN grading system), normal macular OCT scans and peripheral yellowish retinochoroidal infiltrates (2 OD/1 OS), as well as a chorioretinal scar in each eye (Figure 2, A and B). A fluorescein angiography ruled out retinal vasculitis or papillitis and demonstrated hyperfluorescent infiltrates with progressive staining (Figure 2, A and B).

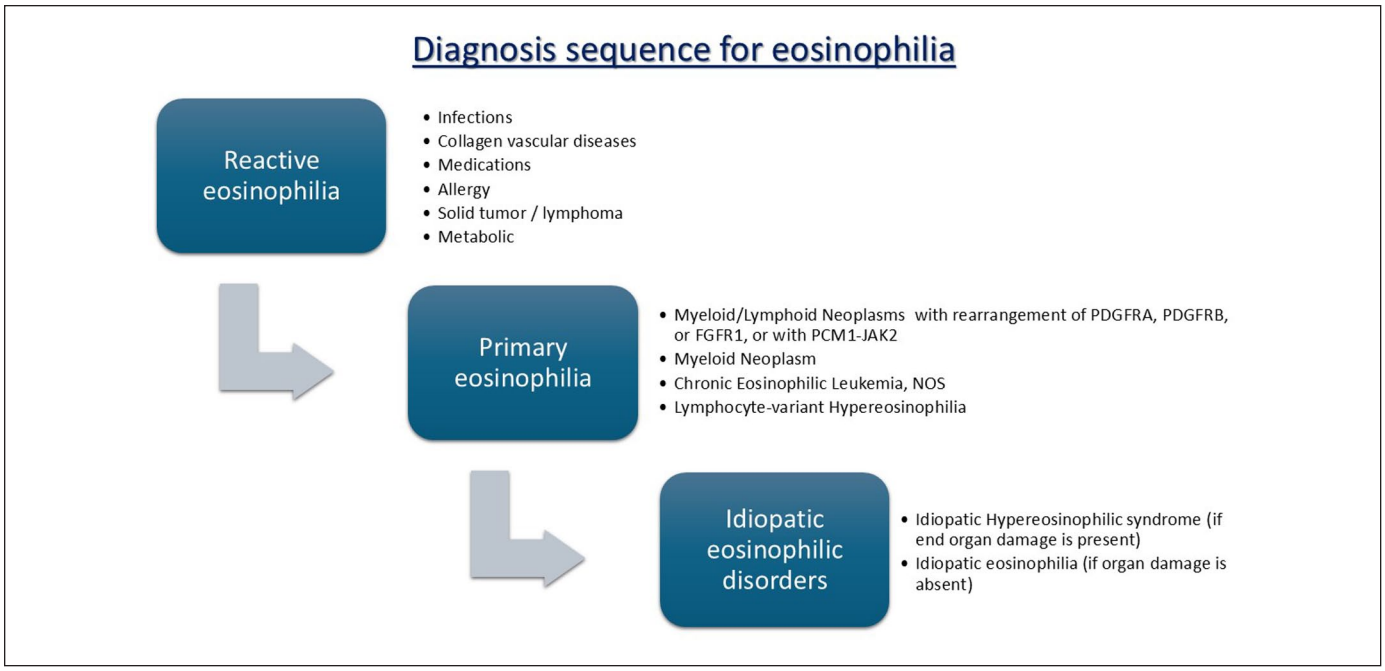

Figure 3. Diagnostic sequence for eosinophilia defined by the World Health Organization.[1]

At the time of presentation, her blood count showed isolated eosinophilia with an AEC of 12.8×10^9/L (0-0.5), and peripheral blood smear confirmed the presence of eosinophilia without blasts. As part of the systemic workup, a thoracoabdominal high-resolution computed tomography (HRCT) scan revealed small areas of ground-glass lung opacities, with no adenopathy. A biopsy of the skin eruption was performed, demonstrating unspecified perivascular dermatitis with eosinophils, with no signs of vasculitis or granulomas.

Multi-organ findings in the context of eosinophilia suggested a differential diagnosis between reactive, primary, or idiopathic HE. Figure 3 shows the recommended diagnostic sequence according to the WHO's latest update on eosinophilic disorders.

The first step was to rule out infectious etiologies to start treatment with steroids. Stool cultures were obtained on 3 consecutive days and were used to rule out the presence of parasites. A PCR analysis of an aqueous humor sample was performed, yielding negative results for *Toxoplasma* and herpes virus. The results of the serological investigations were negative for *Treponema pallidum*, *Tuberculosis*, *Toxoplasma*, *Brucella*, *Borrelia burgdorferi*, *Toxocara, Strongyloide*s, and *Taenia solium*. Viral serologies were negative, including HIV, and the only finding was positive IgG for cytomegalovirus and herpes simplex virus. The patient was started on oral prednisone (1 mg/kg/day) and topical ocular prednisolone (1%).

The patient was evaluated by the rheumatologist of the ocular inflammation unit, who suggested a differential diagnosis of eosinophilia associated with a systemic disease, with a thorough focus on those entities more frequently associated with ocular involvement. Exposure to toxins that could suggest a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was ruled out based on the diagnostic criteria for DRESS, given that the patient had not initiated any new treatment before the increase in AEC. The results of angiotensin-converting enzyme (ACE), serum Ca^{+2}, and 24-hour urine calciuria were in the normal range, therefore ruling out sarcoidosis. Likewise, a differential diagnosis with eosinophilic granulomatosis with polyangiitis (EGPA) was considered. Laboratory tests were negative for rheumatoid factor and antineutrophil cytoplasmic antibodies (ANCA), as well as normal acute phase reactants. The previously performed skin biopsy had shown no evidence of granulomas or necrotizing vasculitis. In addition, a control pulmonary HRCT scan was ordered, which showed that pulmonary infiltrates had disappeared under corticosteroid treatment. Therefore, bronchoalveolar lavage was not performed. Respiratory function tests ruled out bronchial asthma, and a cranial CT scan showed no polyps or alterations in the rhinooropharyngeal structures.

The second step was to rule out primary eosinophilia. The hematology department performed a bone marrow biopsy, showing the presence of up to 35% eosinophils without blasts (Figure 1, B) and no signs of lymphoma infiltration (Figure 1, C). The cytogenetic study showed no PDGFRA, PDGFRB, or FGFR1 rearrangement, nor PCM1-JAK2. Since the patient maintained an AEC $> 1.5 \times 10^9$/L and secondary and primary causes of eosinophilia were ruled out; the diagnosis of HES was assumed.

Under treatment with steroids, the patient showed no recurrence of the skin rashes, resolution of anterior chamber inflammation within 2 weeks, healing of the retinochoroidal infiltrates within 2 months, and complete resolution of vitritis after 3 months (Figure 2, C-F), with a final BCVA of 20/25 OU.

Despite resolution of the multi-organ findings, the number of eosinophils increased as corticosteroid therapy was de-escalated. Treatment with the monoclonal antibody mepolizumab

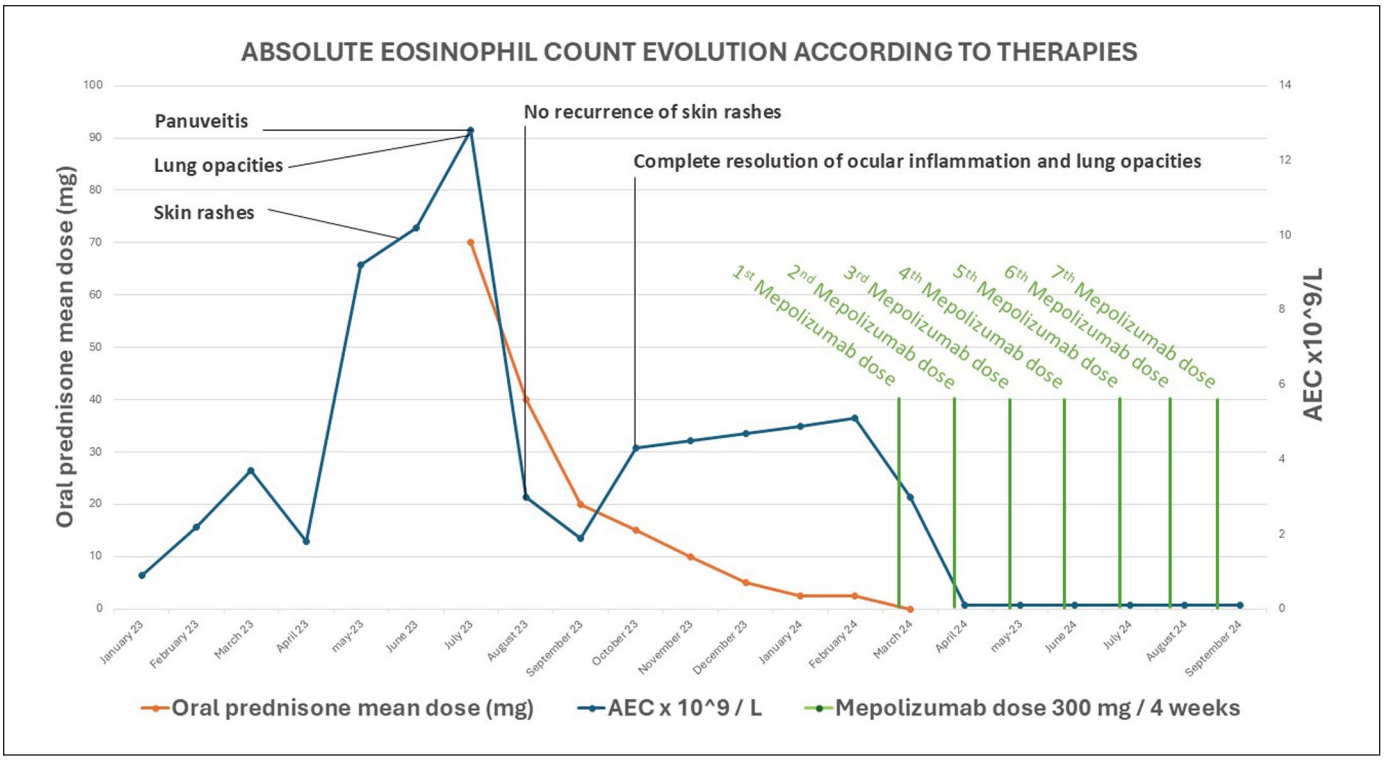

Figure 4. Evolution of the peripheral absolute eosinophil count correlating with the onset of symptoms and therapies.

was initiated, administered at a dose of 300 mg every 4 weeks. The patient showed normalization of the eosinophil count, with an AEC of 0.1×10^9/L after 2 doses of mepolizumab, without adverse effects. Figure 4 shows the evolution of the AEC throughout steroid and mepolizumab treatments.

Discussion

Management of HE requires extensive investigation. The presented case was examined by a multidisciplinary committee, following the diagram in Figure 3, to rule out reactive and primary causes of HE. As for secondary causes, ocular inflammation has been described as being specifically associated with the following reactive conditions: toxocariasis, EGPA, sarcoidosis and DRESS syndrome.[5–8] We ruled out parasitic infection by toxocariasis because of negative serology and incompatible funduscopic presentation. A negative ANCA result was obtained without signs of vasculitis to rule out EGPA. There was no evidence of hilar adenopathy on the CT scan, and the results of ACE and calciuria were within the normal range, ruling out sarcoidosis.

To rule out DRESS syndrome, we reviewed the diagnostic criteria. There is no definite consensus, but the latest reviews tend to use those proposed by the RegiSCAR group.[9–11] Following this system, our patient was defined as a possible case. DRESS usually begins with general malaise and fever, followed by a morbilliform and progressive skin rash that commonly spreads to more than 50% of the total body surface area. Onset of DRESS usually occurs from 2 to 8 weeks after drug intake, although shorter and longer periods have been described.[10] There was no evidence in the patient's history of the introduction of a new drug that could cause DRESS syndrome prior to clinical manifestations in June 2023. She did receive bendamustine-rituximab as well as prophylaxis with acyclovir, trimethoprim-sulfamethoxazole, and folic acid to manage her Waldenström macroglobulinemia, but these medications were started in November 2022. DRESS has been reported with the use of bendamustine, but that case had typical clinical signs and histological findings.[12] Histological findings for DRESS include spongiosis, acanthosis, vacuolization, lymphocytic infiltrate and perivascular predominance, variable presence of eosinophils, atypical lymphocytes and granulomas.[10] The skin eruptions in our case were self-limited, affecting small areas, and the biopsy showed unspecified perivascular dermatitis with eosinophils, with no signs of vasculitis or granulomas.

In the specific context of HES, very few cases of ocular involvement have been described. Two reports have shown retinal vascular alterations that resemble the clinical findings associated with the increase in hematocrit with leukostasis seen in leukemias,[13] and 2 reports have described uveitis. In 2012, Balaskas et al reported the case of a patient with bilateral retinochoroidal infiltrates, identified for the first time at 15 years of age, leaving diffuse scarring that worsened years later with a subfoveal neovascular membrane, causing a final BCVA of 20/160 in 1 eye. Systemically, she presented eosinophilic infiltration in dermatological, pulmonary, pericardial, duodenal, and medullary tissues, as confirmed by biopsies. This patient was only treated with steroids.[3] Later, Ramzan et al described the case of an 8-year-old girl who presented with eosinophilia,

along with altered stool rhythm and fever, without alterations in the thoracoabdominal CT. The patient was monitored by hematology and developed ocular symptoms with bilateral anterior uveitis 20 months later. After establishing the diagnosis of HES, the patient was treated with oral steroids and methotrexate, although she subsequently required the use of imatinib (200 mg daily) due to recurrence of eosinophilia. Despite the treatment, 3 months after starting imatinib and during steroid de-escalation, the patient developed a retinal detachment in her right eye with residual BCVA of light perception. We cannot be certain of the origin of the retinal detachment, nor do we have illustrative images.[4]

In our case, there was involvement of the 3 ocular segments, including retinochoroidal infiltrates, similar to the case described by Balaskas et al.[3] As for correlation with the AEC, the ocular manifestations in our patient were diagnosed during the highest peak of eosinophilia (12.8×10^9/L), as seen in Figure 4. In the case of Ramzan et al,[4] the onset of the episode of bilateral anterior uveitis occurred with eosinophilia levels reaching 5.12×10^9/L. In both cases, the AEC at the time of uveitis onset was classified as severe (AEC $> 5 \times 10^9$/L).[2]

Regarding the pathophysiological mechanism of ocular inflammation in relation to HE, in 2018 Bing et al studied an animal model of experimental autoimmune uveitis (EAU), in which the development of this condition was investigated in the absence of both IFN-γ and IL-17 cytokines. The absence of these cytokines separately failed to suppress the development of EAU, in which affected mice showed a characteristic eosinophilic ocular infiltrate, unlike the mononuclear infiltrate of mice in the control group. These results point to the possibility of intraocular inflammation episodes mediated by granulocyte-macrophage colony-stimulating factor (GM-CSF), the latter acting as the main effector cytokine that drives eosinophilic inflammation.[14]

Treatment of HES is initiated with oral steroids, achieving complete resolution in up to 64% of patients in some retrospective series.[1] In cases of clinical or hematologic relapse, hydroxyurea or interferon-α have been previously used. The monoclonal antibody mepolizumab, directed against interleukin-5 and thus interfering in the differentiation and activation of eosinophils, was approved by the FDA in 2020 for the management of HES.[15] The dose used in HES is 300 mg every 4 weeks, with subcutaneous administration. Lower HES flare rates have been observed with mepolizumab (28%) compared to placebo (53%), with a similar rate of non-serious side effects, emerging as a safe and effective therapeutic alternative.[16]

Conclusions

We present a challenging case of severe HE associated with bilateral panuveitis, including retinochoroidal infiltrates. The diagnosis of HES requires an exhaustive and sequential multidisciplinary study to rule out reactive and primary causes of eosinophilia.[1] Infections and drug-related reactions must always be considered. Obtaining histologic samples of accessible tissues is important to address the differential diagnosis.[10]

It has been demonstrated that ocular inflammation in the absence of IFN-γ or IL-17 cytokines can be mediated by eosinophils in an animal model.[14] Unlike the pediatric cases of HES-associated uveitis described in the literature, we observed a favorable response to steroid treatment. In cases of clinical or hematologic relapse following initial steroid therapy, new drugs directed against interleukin-5 are available as a therapeutic option to interfere in the differentiation and activation of eosinophils.[1,16]

Ethical Approval

Ethical approval was not sought for the present study because no patient-identifying information was included.

Statement of Informed Consent

Written informed consent was not obtained for the present report because no information was included.

Declaration of Conflicting Interests

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