



Hypereosinophilic syndrome—a rare adverse event of anti-cytokine treatment in rheumatoid arthritis resolved after Janus kinase inhibitor therapy

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Abstract

Eosinophilia is uncommon in early rheumatoid arthritis (RA). The most frequent causes of hypereosinophilia during RA treatment are atopic eczema, allergy, helminth infection, haematological malignancy and drug-associated complications. The pathogenesis of this abnormality associated with anti-cytokine therapy is still unknown. We report the case of a young woman with RA and eosinophilia accompanied by systemic symptoms such as dyspnoea, fluid retention and eosinophilic vasculitis. An interesting observation was the persistence of eosinophilia during treatment with various biologics and its normalization after switching to the Janus kinase inhibitor baricitinib.

Keywords Anti-cytokine therapy · Baricitinib · Eosinophilia · Rheumatoid arthritis · Vasculitis

Introduction

Peripheral eosinophilia is characterized by an absolute eosinophil count (AEC) of more than 450–550/mm³ or 5% of peripheral blood leukocytes [1]. Hypereosinophilia is a condition with an AEC higher than 1500/mm³ and hypereosinophilic syndrome (HES) is a disorder marked by overproduction of eosinophils (AEC greater than 1500/mm³) and organ dysfunction attributable to eosinophilia. Affected target organs can include the lungs, heart, skin, kidneys and brain. High AEC may be caused by numerous conditions, mostly allergic, infectious (e.g. parasites, helminths), inflammatory, skin diseases (e.g. dermatitis herpetiformis),

Addison's disease and neoplastic disorders (e.g. metastatic cancer, haematological malignancies).

Eosinophilia is a rare abnormality in rheumatic disorders. The most common rheumatic inflammatory diseases that present with hypereosinophilia are eosinophilic fasciitis, eosinophilic granulomatosis with polyangiitis, dermatomyositis, Sjögren's syndrome and systemic sclerosis. The reported case describes a patient with seropositive rheumatoid arthritis (RA) who developed eosinophilia with dramatic organ involvement as the presentation of HES during biologic treatment.

Case report

A 39-year-old obese woman (body mass index 43.6 kg/m²) with a previous history of drug allergy (tetracycline rash) and diagnosis of seropositive RA (rheumatoid factor and anti-citrullinated protein autoantibody positivity) in 2013 at the age of 39 years was initially treated with methotrexate (20 mg/week) and prednisolone (10 mg/day). In July 2014, she was switched to biologics because of inadequate response to conventional therapy. Her DAS28-CRP (Disease Activity Score-28 calculated with C-reactive protein) was 6.43. The initial complete blood count (CBC) showed slight anaemia (haemoglobin, 1.12 g/dl; erythrocyte count, $4.05 \times 10^{12}/l$; platelets, $298 \times 10^9/l$) and the leukocyte count (including

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differential) was normal (white blood cells, $6.5 \times 10^9/l$; neutrophils, $4.16 \times 10^9/l$; lymphocytes, $1.52 \times 10^9/l$; monocytes, $0.42 \times 10^9/l$; eosinophils, $0.4 \times 10^9/l$; basophils, $0.01 \times 10^9/l$).

She was started on golimumab treatment, administered subcutaneously at a dose of 50 mg once a month, and showed a good response: her DAS28-CRP was 3.68 after 3 months. Methotrexate treatment was co-administered and the dose of prednisolone was tapered down to 5 mg once daily. Two months later, a skin biopsy was taken from recently developed, slightly painful, cutaneous nodules on her fingers. A diagnosis of granuloma annulare was confirmed histologically and was probably related to anti-tumour necrosis factor (anti-TNF) therapy.

In January 2015 (after 6 months of golimumab treatment), the patient presented with a 1-week history of dyspnoea, erythema and swelling of the face, retention of fluid and weight gain (6 kg/week), without evidence of any suspected environmental exposure. Eosinophilia ($4.31 \times 10^9/l$) and mild leukocytosis ($11.97 \times 10^9/l$) were found in the CBC. The patient underwent additional laboratory evaluation and imaging methods in the differential diagnostic process to identify the aetiology of the symptoms: chest X-ray, high-resolution computed tomography, computed tomography pulmoangiography, echocardiography, abdominal ultrasonography, spirometry, tests to exclude infection (including helminths), ear, nose, and throat examination, antinuclear antibody test, anti-ds-DNA test, antineutrophil cytoplasmic antibody test, IgE test, basophil activation test, complete haematological work-up with bone marrow examination, flow cytometry and cytogenetic analysis. The presumptive diagnosis of HES was made, considered to be an allergic reaction to the medication, possibly golimumab. The acute state was managed with intravenous hydrocortisone, furosemide and antihistamines. Golimumab treatment was discontinued. Subsequently, her RA was not optimally controlled with systemic corticosteroids (prednisolone, 7.5 mg/day) and methotrexate (20 mg/week) but over the next few weeks, her eosinophil count dropped to $1.59 \times 10^9/l$.

In March 2015, we initiated treatment with certolizumab pegol, subcutaneously at a maintenance dose of 200 mg every 2 weeks (concomitant medication: methotrexate and prednisolone). The eosinophil count was in the range 0.87 – $6.45 \times 10^9/l$ during administration of this anti-TNF medication. After 3 months of treatment with certolizumab, DAS28-CRP was 4.53 (tender joints count 4; swollen joints count 3; CRP 32.2 mg/l, VAS general health 50 mm). Clinical findings of arthritis were mild but the laboratory parameters of inflammation were higher (certolizumab treatment was started 3 months after the last golimumab application). We decided to stop treatment because of an inadequate response and the persistence of hypereosinophilia. In September 2015, tocilizumab (anti-IL-6R monoclonal antibody) was started intravenously at a dose of 800 mg monthly (the patient's weight was 140 kg), with a good response (DAS28-CRP was 2.93) after

3 months of treatment. However, because the peripheral vein was inaccessible, we continued with subcutaneous administration of tocilizumab (162 mg monthly). Two months after tocilizumab treatment, only slight eosinophilia was observed ($1.01 \times 10^9/l$). Combined therapy with methotrexate (15 mg weekly) and prednisolone (5 mg once daily) was added because of a suboptimal therapeutic effect of anti-IL-6R treatment (possibly partially due to the severe obesity). At this time, petechiae and purpura were observed on her fingers and a skin biopsy was taken (Fig. 1). Histological examination revealed perivascular infiltration of lymphocytes and eosinophils in the dermis. The perivascular infiltration had an appearance of eosinophilic vasculitis, without signs of necrotizing vasculitis (Fig. 2). During tocilizumab treatment (September 2015–June 2019), the eosinophil count escalated to $13.22 \times 10^9/l$ but there was low disease activity (Fig. 3). The patient had neither systemic signs nor symptoms of allergy; also, the skin lesions on her fingers were not painful and had varying intensity of appearance. After 4 years, the RA worsened, with high clinical disease activity (DAS28-CRP was 5.56). A possible reason for the lack of tocilizumab effectiveness later on was the switch to subcutaneous administration and the low medication concentration for a morbidly obese patient (the patient lost weight by dieting but was still overweight—121 kg). Another possibility is ADA formation, but with tocilizumab treatment, the ADA concentrations are generally low.

Baricitinib (5 mg daily, orally) was started in June 2019 and this resulted in rapid normalization of the eosinophil count within 3 months ($0.19 \times 10^9/l$). The patient is still being treated with baricitinib and the RA symptoms are well controlled, along with a completely normal CBC (Fig. 3).

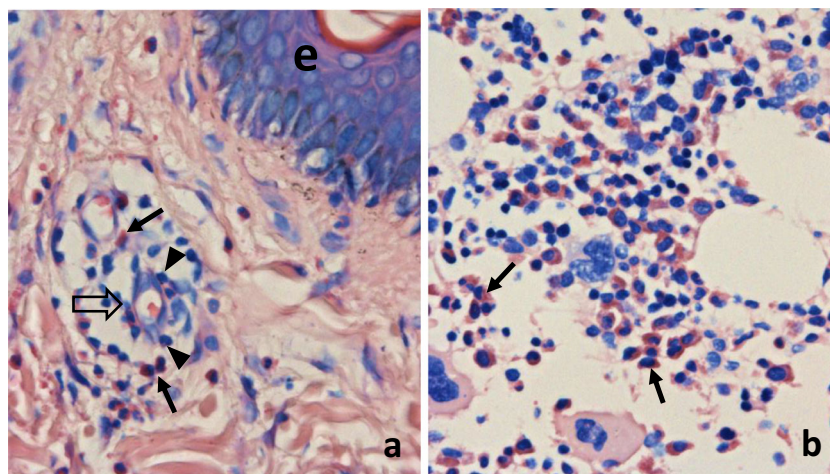
Discussion

Peripheral blood eosinophilia is infrequent in early RA. The prevalence of baseline eosinophilia in RA was 3.2% in a



Fig. 1 Petechiae and purpura on patient's fingers

Fig. 2 Histological findings of skin lesions on the finger and bone marrow



French ESPOIR cohort and was mild and transient in most patients [2]. Some investigators have reported that eosinophilia may occur in severe RA [3]. The most common causes of elevated AEC during RA treatment are allergy, helminth infection, haematological malignancy and drug-associated complications. Commonly, the incidence of drug-induced eosinophilia is low (0.1% reported by Rothenberg) [4]. Some authors have described eosinophilia in RA and juvenile idiopathic arthritis patients treated by methotrexate and gold therapy [5, 6]. In recent decades, we have seen an explosion of anti-cytokine therapy in rheumatology. Complications associated with the administration of biological agents include immune-mediated adverse events caused by immunogenicity, which are usually presented as infusion reactions due to the formation of anti-drug antibodies (ADAs), paradoxical reactions (e.g. vasculitis-like events), lupus-like events, and etc.

Hypereosinophilia associated with biologic treatment is rare. Even when a laboratory abnormality is found, only in a few cases is the clinical symptomatology associated with pathological CBC. The mechanism of this adverse event is still unknown but the most common cause is anti-TNF or anti-IL-

6R treatment. Nakahigashi et al. reported a case of eosinophilic necrotizing vasculitis presented with cutaneous digital eosinophilic vasculitis and massive eosinophilia, possibly related to etanercept therapy [7]. Azuma et al. presented an RA patient with continuous eosinophilia and skin symptoms during treatment with different biologics—adalimumab, infliximab, tocilizumab—but these symptoms disappeared after switching to golimumab [8]. Their review of the literature cited adalimumab as the most common biologic associated with the adverse event of eosinophilia, but it is also known that adalimumab is the most frequently used anti-TNF agent with the widest indications for the treatment of various autoimmune disorders. The authors declare that golimumab is a molecule with lower immunogenicity due to its structure (it is a fully human antibody) and their theory explains that eosinophilia is the consequence of drug immunogenicity. In our patient's case, golimumab was the trigger for HES. The patient showed high AEC during treatment with two anti-TNF biologics (golimumab and certolizumab pegol) and an anti-IL-6R (tocilizumab) agent. The AEC normalized only after switching to the Janus kinase (JAK) inhibitor baricitinib, which is a small molecule. The biologics used in the treatment of our patient were different in their mechanisms of activity (anti-TNF and anti-IL-6R) and their structure (golimumab is a full human antibody, whereas certolizumab pegol and tocilizumab are humanized monoclonal antibodies). Golimumab belongs to the group of monoclonal antibodies having lower immunogenicity, with 6.5% ADA development in a clinical trial assessing the efficacy and safety of golimumab in RA patients [9]. Other recent works using more sensitive methods (drug-tolerant enzyme immunoassay) have detected markedly higher concentrations of ADA against golimumab (31.7%) [10]. The ADA level in patients treated with certolizumab pegol is similar, at 37% [11]. ADA concentrations in a group of patients treated with subcutaneous tocilizumab were low (3.5%) and were not detected in intravenous therapy in a Japanese study [12].

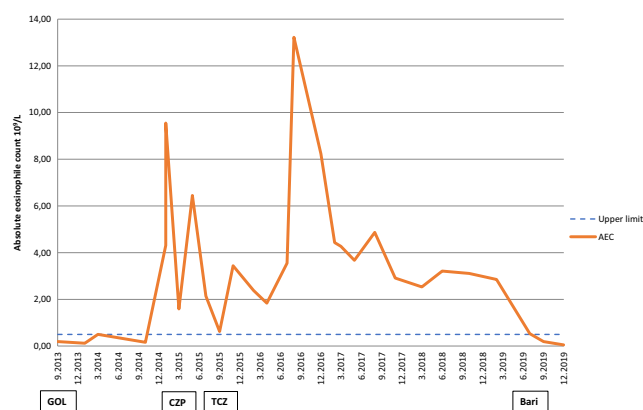


Fig. 3 Graph of eosinophil count over time. GOL – golimumab, CZP – certolizumab pegol, TCZ – tocilizumab, Bari – baricitinib, AEC – absolute eosinophil count

There are other hypotheses suggesting that IgE-mediated drug hypersensitivity or cytokine-mediated inhibition of eosinophil apoptosis can cause eosinophilia [13]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a haemopoietic growth factor and its contribution to the pathogenesis of RA is well known. Previous studies showed that patients responding to TNF inhibitors tend to have a high frequency of T cells that produce GM-CSF [14]. IL-3, IL-5 and GM-CSF are T cell-derived cytokines that share a common β subunit and inhibit eosinophil apoptosis regulated by tyrosine phosphorylation [15, 16]. A work published by Simon et al. demonstrated that activation of freshly isolated human blood eosinophils by GM-CSF is associated with increased phosphorylation of JAK2 [14]. Baricitinib is an inhibitor of JAK, blocking subtypes *JAK1* and *JAK2*. The above-described pathogenesis offers an explanation for the beneficial effect of baricitinib on the hypereosinophilia reported in our patient.

Conclusion

A wide range of immunologically mediated adverse events induced by biologics have been reported, such as eosinophilia associated with anti-TNF and anti-IL6-R therapy. This case describes a patient with RA complicated with severe eosinophilia and cutaneous digital eosinophilic vasculitis, probably related to biologic treatment. The precise pathogenesis of this adverse event is not fully understood but eosinophil apoptosis inhibition by GM-CSF and activated JAK2 offers a reasonable explanation. Switching to a JAK2 inhibitor could be a helpful alternative in the therapeutic management of RA patients with eosinophilia related to biologics. The presented case is the first report to confirm this theoretical assumption in clinical practice.

Compliance with ethical standards

Disclosures None

References

- Kovalszki A, Weller PF (2016) Eosinophilia. *Prim Care* 43(4):607–617
- Guellec D, Milin M, Cornec D, Tobon GJ, Marhadour T, Jousse-Joulin S, et al (2015) Eosinophilia predicts poor clinical outcomes in recent-onset arthritis: results from the ESPOIR cohort. *RMD Open* 2015; published on 15 July. <https://doi.org/10.1136/rmdopen-2015-000070>
- Panush RS, Franco AE, Schur PH (1971) Rheumatoid arthritis associated with eosinophilia. *Ann Intern Med* 75(2):199–205
- Rothenberg ME (1998) Eosinophilia. *N Engl J Med* 338(22):1592–1600
- Savolainen HA, Leirisalo-Repo M (2001) Eosinophilia as a side-effect of methotrexate in patients with chronic arthritis. *Clin Rheumatol* 20(6):432–434
- Edelman J, Davis P, Gwen ET (1983) Prevalence of eosinophilia during gold therapy for rheumatoid arthritis. *J Rheumatol* 10:121
- Nakahigashi K, Egawa G, Miyachi Y, Kabashima K (2014) Digital vasculitis with eosinophilia possibly associated with etanercept therapy. *Acta Derm Venereol* 94(2):239–240
- Azuma N, Matsui K, Hashimoto N, Yoshikawa T, Sano H (2017) Successful switch to golimumab for eosinophilia and skin symptoms related to multiple biologics in a patient with rheumatoid arthritis. *Intern Med* 56(12):1585–1590
- Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, Hsia EC, Han J, Wagner C, Xu Z, Visvanathan S, Rahman MU (2008) Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 58(4):964–975
- Leu JH, Adedokun OJ, Gargano C, Hsia EC, Xu Z, Shankar G (2019) Immunogenicity of golimumab and its clinical relevance in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. *Rheumatology (Oxford)* 58(3):441–446
- Jani M, Isaacs JD, Morgan AW, Wilson AG, Plant D, Hyrich KL, Chinoy H, Barton A, BRAGGSS (2017) High frequency of anti-drug antibodies and association of random drug levels with efficacy in certolizumab pegol-treated patients with rheumatoid arthritis: results from the BRAGGSS cohort. *Ann Rheum Dis* 76(1):208–213
- Ogata A, Tanimura K, Sugimoto T, Inoue H, Urata Y, Matsubara T, Kondo M, Ueki Y, Iwahashi M, Tohma S, Ohta S, Saeki Y, Tanaka T, the Musashi Study Investigators (2014) Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 66:344–354
- Simon HU, Blaser K (1995) Inhibition of programmed eosinophil death: a key pathogenic event for eosinophilia? *Immunol Today* 16: 53–55
- Bystrom J, Clanchy FI, Taher TE (2017) Response to treatment with TNF α inhibitors in rheumatoid arthritis is associated with high levels of GM-CSF and GM-CSF+ T lymphocytes. *Clin Rev Allergy Immunol* 53(2):265–276
- Simon HU, Yousefi S, Dibbert B, Levi-Schaffer F, Blaser K (1997) Anti-apoptotic signals of granulocyte-macrophage colony-stimulating factor are transduced via JAK2 tyrosine kinase in eosinophils. *Eur J Immunol* 27(12):3536–3539
- Yousefi S, Hoessli DC, Blaser K, Mills GB, Simon HU (1996) Requirement of Lyn and Syk tyrosine kinases for the prevention of apoptosis by cytokines in human eosinophils. *J Exp Med* 183(4): 1407–1414

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