

Hypereosinophilia and Seroconversion of Rheumatoid Arthritis

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Received: 13 February 2014 / Revised: 23 February 2014 / Accepted: 25 February 2014 / Published online: 8 March 2014
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Abstract At the intersection of atopy and autoimmunity, we present a patient with seronegative rheumatoid arthritis (RA) who developed hypereosinophilia, without evidence of other etiologies, as she became rheumatoid factor (RF) positive. Although the magnitude of eosinophilia in patients with RA has been thought to reflect the severity or activity of the RA, in our patient, eosinophilia developed at a time when the patient's synovitis was well controlled. Although eosinophilia may reflect associated drug hypersensitivity, discontinuation of the medications utilized to control our patient's disease, adalimumab and methotrexate, did not promote clinical improvement. Probably the most curious aspect of our patient was the concomitant development of rheumatoid factor seropositivity in the setting of previously seronegative RA. The temporal relationship between the development of peripheral eosinophilia and seroconversion suggests a possible connection between these events. We speculate that the T cell cytokine production that can induce eosinophilia may simultaneously activate RF production.

Keywords Cytokines · Eosinophilia · Rheumatoid arthritis · Rheumatoid factor · Tyrosine kinase

Introduction

A link between severe rheumatoid arthritis (RA) and eosinophilia has been appreciated for the past 40 years [1, 2], but the mechanisms of this association are still not well understood. Although seen in eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) and other specific inflammatory conditions, eosinophilia is not a typical manifestation of autoimmunity, which classically has a Th1 or Th17 pathogenesis. Eosinophilia is more commonly associated with Th2 processes such as allergy, drug hypersensitivity reactions or parasitic infections, and with hematologic malignancies [3].

Here, we present a patient with seronegative RA whose disease was well controlled on adalimumab and methotrexate, who developed dramatic hypereosinophilia, without an identifiable etiology and simultaneously converted to rheumatoid factor (RF) seropositivity.

Case Report

An 86-year-old woman originally presented with symmetric inflammatory polyarthritis 18 years earlier. Laboratory studies included ESR 94 mm/h; C-reactive protein 23 mg/dl (normal <0.8 mg); RF was not detected. Radiographs only revealed mild degenerative changes of the DIPs and first CMC joints. Arthrocentesis of the right wrist found mildly inflammatory fluid, without urate or calcium pyrophosphate crystals. Satisfying four of seven features of the 1987 ACR (ARA) classification criteria for rheumatoid arthritis (RA), a presumptive diagnosis of seronegative RA was made. Her symptoms worsened on NSAIDs and low-dose oral prednisone was begun. Treatment with sulfasalazine 2,000 mg daily for 6 months was ineffectual. Methotrexate was substituted, and after 4 months of therapy at 17.5 mg weekly, her synovitis was

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well controlled and prednisone was tapered. Five years later, she developed recurrent synovitis, successfully managed with addition of infliximab. After 4 years, due to logistical difficulties, she was switched to adalimumab, while continuing methotrexate 15 mg weekly, with good clinical disease control. There was no evident radiographic progression. Repeat RF and anti-citrullinated peptide antibody (ACPA) were negative.

She continued to feel well for another 2 years, until she developed daily crops of urticaria, primarily involving her upper arms, legs, and face, and angioedema, involving her scalp, periorbital regions, forearms, hands, and feet. Because of concern for drug hypersensitivity, methotrexate and adalimumab were discontinued. Various anti-histamines, doxepin, montelukast, and subsequently hydroxychloroquine were ineffective. Studies revealed progressive leukocytosis with eosinophilia, ultimately reaching a maximum total white cells of $28,300/\text{mm}^3$, with $24,100$ eosinophils/ mm^3 . RF became detectable, ranging between 588 and 1,190 IU (normal <14 IU); ACPA, anti-MPO, anti-PR3, ANA, and anti-cardiolipin antibodies were all negative. Tests for HIV, C3, C4, vitamin B12, and serum tryptase were all normal or negative; IgE was 385 mg/dl (normal <100); on several occasions, type III cryoglobulins were measured and immunoelectrophoresis revealed a small IgM λ monoclonal spike. Evaluation for other causes of eosinophilia, including allergy testing and stool ova and parasites, was unrewarding. A skin biopsy revealed severe dermal swelling with superficial and mid-dermal perivascular and interstitial mixed inflammatory infiltrate with predominant lymphocytes, histiocytes, and eosinophils; no vasculitis or granulomas were observed; immunofluorescent staining for vascular deposits of immunoglobulin and complement was negative. Due to the persistence of urticaria and angioedema, systemic treatment with corticosteroids was reinstituted. Although her synovitis remained quiescent on prednisone 20 mg, she continued to note urticaria and angioedematous sites; her peripheral eosinophil count remained markedly elevated ($>20,000/\text{mm}^3$). A course of cyclosporine was initiated but discontinued due to developing renal insufficiency. ENT examination, chest imaging, pulmonary function testing, and echocardiography were not indicative of EGPA or end-organ effects of hypereosinophilic syndrome (HES). Bone marrow examination revealed normocellular marrow with increased M:E ratio due to the presence of abundant mature appearing eosinophils; no spindle-shaped mast cells were seen. Flow cytometry revealed normal T lymphocyte phenotyping. Cytogenetic analysis showed no chromosomal abnormalities. TCR gene rearrangements and evidence of the FIP1-like-1 (FIPL1)/platelet-derived growth factor receptor gene (PDGFRA) mutation were not identified.

With prominent skin manifestations and the absence of cytogenetic abnormalities, a presumptive diagnosis of

lymphocytic variant of HES was made. Desiring to avoid the use of interferon- α and with anecdotal reports of its utility in treating RA [4, 5], the patient was managed with imatinib mesylate 400 mg daily. Within 3 weeks of starting treatment, the patient noted marked reduction of urticaria and angioedema. Due to severe nausea and peripheral edema, imatinib was first reduced to 100 mg daily and then discontinued after 14 weeks. Peripheral eosinophil count diminished to $1,820/\text{mm}^3$. Prednisone was tapered as urticaria and angioedema resolved, despite the relatively short duration of imatinib therapy. Within several months, she developed recurrent synovitis of the hands and wrists, without worsening of urticaria. After a 1-year hiatus, methotrexate was resumed and the patient's synovitis remained controlled for the subsequent 5 years on methotrexate 15 mg weekly and prednisone 2.5 mg daily. RF ranged from 141 to 267 IU, with negative ACPA, cryoglobulins, and monoclonal protein. Her eosinophil count has stayed below $2,300/\text{mm}^3$ range, and she continued to have rare solitary urticarial lesions.

Discussion

Although commonly seen in EGPA syndrome and certain other rheumatic diseases where eosinophils have been directly implicated in their pathogenesis [6], eosinophilia is not a common finding in inflammatory rheumatologic diseases, although it has been reported in specific case series in RA [7]. Eosinophils are produced from hematopoietic stem cells in the bone marrow. Their proliferation and differentiation are stimulated in the presence of interleukin-5 (IL-5), as well as IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Not only have eosinophils been shown to proliferate in the setting of parasitic infections and allergic responses but also they have been thought to play a role in immunoregulatory and homeostatic processes [8].

It has been documented by Panush et al. and others that eosinophilia may occur in severe seropositive RA [1, 2, 9], but it is underappreciated that increasing RF titers have been demonstrated to directly correlate with eosinophilia in other non-RA processes, such as chronic eosinophilic pneumonia [10]. Some patients with severe asthma have developed increased RF titers concomitant with hypereosinophilia [11]. These observations suggest that similar pro-inflammatory conditions may initiate eosinophil proliferation as well as RF production. Alternatively, initiation of one of these processes may activate the other.

Injection site and infusion reactions commonly occur after treatment with TNF- α antagonists [12]. Rarely, true allergic inflammatory responses have been documented, as in a recent report of a patient who developed a mild subcutaneous reaction upon initial exposure to adalimumab and later developed eosinophilic cellulitis (Wells' syndrome) upon second

exposure [13]. Eosinophilic cellulitis has also been noted in response to etanercept [14]. Furthermore, a patient with a 22-year history of RA treated with methotrexate and prednisone developed subacute prurigo and systemic eosinophilia upon discontinuation of methotrexate and initiation of treatment with infliximab. Symptoms resolved with increased systemic corticosteroids and discontinuation of infliximab but returned a year later when etanercept therapy was initiated. These symptoms were attributed to a drug reaction considering the temporal relationship between initiation of the medications and symptoms [15]. Conversely, a role for TNF- α antagonists in the treatment of asthma and alleviation of eosinophilia has been suggested in mouse models and some pre-clinical studies [16].

Rather than representing an allergic response to drug therapy, we believe that our patient developed HES superimposed on her pre-existent, well-controlled RA. HES was described in 1968 by Anderson and Hardy, but diagnostic criteria for the syndrome were not developed until 1975 by Chusid, et al. [17]. These criteria include (1) persistent eosinophilia ($1,500/\text{mm}^3$) for at least 6 months, (2) lack of specific cause, and (3) evidence of organ involvement [18]. Further classification of these disorders into “leukemic” vs. “hypersensitivity reaction” forms or “myeloproliferative” vs. “lymphocytic” forms have been discussed. Lymphocytic forms are typically driven by production of eosinophil growth factors like IL-3 or IL-5 by T cells to lead to a secondary polyclonal hypereosinophilia. Myeloproliferative forms of HES exhibit clinical or hematologic signs of malignancy, and the basis for the eosinophilia is a mutation in multipotent precursor cells, not cytokine production, although overlap may exist [19]. By these criteria, our patient likely exhibited the lymphocytic form of HES. Although she did not have a known mutation to explain the eosinophilia or evidence of a hematologic malignancy, imatinib therapy adequately treated her hypereosinophilia, urticaria, and angioedema. This response is consistent with other studies that have shown that patients without the FIPL1/PDGFR α fusion can respond to imatinib (albeit typically at doses greater than those administered to our patient) supporting a role for other imatinib-sensitive tyrosine kinase activities in promoting HES [3, 20, 21]. The effectiveness of imatinib for treatment of RA has been demonstrated in animal models, ex vivo studies and in small clinical trials [4, 22, 23]. Although the exact mechanism of action remains unknown, imatinib has well-documented inhibitory effects on several cellular responses that help drive synovitis, pannus formation, and joint destruction, including mast cell c-Kit signaling, TNF- α release, macrophage c-Fms activation and cytokine production, fibroblast PDGFR signaling and proliferation, Akt signaling, and the JAK-STAT pathways [22–24].

One might argue that a single, unknown trigger of immune activation may have induced both production of RF and eosinophilia simultaneously in our patient. It has been

suggested that T cell activation may promote eosinophilia and B cell RF production [10]. Interestingly, the low affinity, IgM class of RF is primarily produced by CD5 $^{+}$ B cells [25], which can be activated in a T-independent manner. These cells, also called B-1 B cells, have been shown to constitutively express the IL-5R α chain in the mouse, and their proliferation and survival have been shown to be regulated by IL-5 [26]. It is possible that in settings where hypereosinophilia is induced by means of IL-5 production by T cells, or potentially innate lymphoid cells as has been shown in mice [27], IL-5's role in activating B-1 B cells might directly contribute to RF production in humans.

Although severity or activity of RA has been linked with the development of eosinophilia in the older literature, in the case of the patient presented here, we believe that the conditions that promoted development of HES resulted in the development of RF seropositivity, as has been seen in other clinical settings, potentially through mechanisms that involve T cell-mediated IL-5 stimulation of RF producing B cells.

Role of the Funding Source None.

Conflict of Interests None.

Support None.

Disclaimers None.

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