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Persistent eosinophilia in rheumatoid arthritis: a prospective observational study

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Abstract

Eosinophilia is an uncommon manifestation in Rheumatoid arthritis (RA), and there is a paucity of data regarding the relationship of eosinophilia with disease-related factors. We prospectively evaluated the clinical and disease-specific characteristics of RA patients with eosinophilia. Consecutive patients with RA with an absolute eosinophil count ≥ 500/mm^3 without an apparent cause for eosinophilia, were investigated for parasitic infestation. Patients with a definite parasitic infestation received targeted therapy, and the rest were treated with albendazole empirically. The RA disease-specific characteristics of the patients with persistent eosinophilia were compared with the patients without eosinophilia. Of the 160 patients with eosinophilia, 30 patients (19%) had allergic diseases, six patients had bronchiectasis, and one patient had hypereosinophilia of undetermined significance. Intestinal helminthiasis was found in 34 patients (21%). Eosinophilia was unexplained in 89 patients (56%) and it resolved after empirical albendazole therapy in about two-thirds (58 patients). Thirty-one patients had persistent eosinophilia. Nonsteroidal anti-inflammatory drug and disease-modifying antirheumatic drug modification did not show any effect on eosinophilia. The disease-related characteristics were similar between patients with persistent eosinophilia and those without eosinophilia. Eosinophilia is due to secondary causes in the majority of RA patients, and the most common cause in our setting is an intestinal helminthic infection. Persistent eosinophilia in our cohort of RA did not indicate a more severe disease phenotype.

Keywords Rheumatoid arthritis · Eosinophilia · Intestinal helminthiasis · Albendazole · Disease activity

Abbreviations

ACPA	Anti-citrullinated protein antibodies
AEC	Absolute eosinophil count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DAS28	Disease activity score in 28 joints

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DMARDs	Disease-modifying antirheumatic drugs
DRESS	Drug rash with eosinophilia and systemic symptoms
ELISA	Enzyme-linked immunosorbent assay
ESPOIR	Etude et Suivi des POlyarthrites Indifférenciées Récentes
ESR	Erythrocyte sedimentation rate
FIP1L1-PDGFRA (F/P)	Fip1-like 1-platelet-derived growth factor receptor alpha fusion gene
HCQ	Hydroxychloroquine
HEus	Hypereosinophilia of undetermined significance
IHAQ	Indian version of the Health Assessment Questionnaire
ILD	Interstitial lung disease
LEF	Leflunomide
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
PDGFRB	Platelet-derived growth factor receptor beta
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SJ	Swollen joint
SSZ	Sulfasalazine
TJ	Tender joint
VAS	Visual analog scale

Introduction

Eosinophilia has been described in various rheumatic disorders. Eosinophilia is common and plays a clinical and pathological role in entities like eosinophilic granulomatosis with polyangiitis (EGPA), and diffuse fasciitis with eosinophilia (DFE). Eosinophilia had also been described as an uncommon manifestation in diseases like systemic sclerosis, Sjogren's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, and dermatomyositis [1]. In any patient with a rheumatic disorder where eosinophilia is not a common manifestation, care should be taken to evaluate for other causes of eosinophilia like medications, allergic diseases, parasitic infestation, or hematologic disorders.

The prevalence of eosinophilia in patients with RA varies from 3.2 to 21.6% depending on the population studied, criteria used for the diagnosis and the nature of the study [2–4]. It has been shown that common secondary causes of eosinophilia, such as parasitic infestations or allergic diseases, can occur at different frequencies in RA patients according to the population studied [2, 3]. Parasitic infestation, especially intestinal helminthiasis, has been found to be highly prevalent in Indian population [5–7]. Socioeconomic realities such as lack of access to safe drinking water, lack of proper stool disposal systems, improper handling of vegetables, and improper cooking of food, are few among the many risk factors contributing towards such parasitic infections. Moreover, RA patients are especially prone to infections, either as a result of the disease per se, or due to immunosuppression encountered during therapy with disease-modifying antirheumatic drugs (DMARDs), and, in general, the incidence of infections has been found to be about twofold higher compared to the general population [8–10]. Hypersensitivity reaction to the therapeutic agents used in RA may also cause eosinophilia, and the manifestations may vary, ranging from asymptomatic eosinophilia to life-threatening events like drug rash with eosinophilia and systemic symptoms (DRESS) [11–15]. Drug-induced eosinophilia tends to normalize once the offending agent is stopped [11, 13, 15].

Few studies have analyzed the significance of eosinophilia in RA. Earlier studies suggested that eosinophilia might predict a more severe disease phenotype, and more recently, eosinophilia was found as a predictor of poor clinical outcome in early arthritis [3, 16, 17]. Albeit there are different observations where no association between eosinophilia and RA severity could be found [2, 4]. However, there is a paucity of data regarding the relationship of eosinophilia with disease-related factors in RA, and the studies available are primarily in the form of case reports, case series, and cross-sectional studies. Moreover, eosinophilia in RA has never been prospectively evaluated in Indian patients.

Hence, we conducted this prospective observational study to evaluate the prevalence and etiology of eosinophilia in RA patients, and to study its relationship with disease-related characteristics.

Methods

Study design

This was a prospective observational study, wherein patients were followed up for a minimum period of 1 year. This study was conducted over 2 years at the Department of Clinical Immunology at a tertiary care hospital in southern India. Patients were enrolled up from February 2015 to January 2016, and followed up till January 2017.

Patient population

Consecutive adult patients (age ≥ 18 years) who fulfilled the 2010 ACR-EULAR criteria for the classification of RA were included in this study [18]. Those patients with an absolute eosinophil count (AEC) of ≥ 500/mm^3 were worked up for

etiology of eosinophilia through detailed history, physical examination, and lab investigation. The patients with an apparent cause of eosinophilia like atopic diseases (allergic rhinitis, atopic dermatitis, and bronchial asthma), bronchiectasis, and hypereosinophilia syndrome were excluded from such further evaluation for parasitic infestation.

Study protocol

Baseline demographic parameters were documented. Clinical data regarding RA such as duration of disease, disease activity based on the swollen joint (SJ) count, tender joint (TJ) count, patient VAS (visual analog scale) for pain and global health, erythrocyte sedimentation rate (ESR) and Disease Activity Score-28 ESR (DAS28 ESR) were obtained. The functional disability assessment was done using the Indian version of the Health Assessment Questionnaire (IHAQ) [19]. Symptoms and signs of extra-articular features such as xerostomia and xerophthalmia, subcutaneous nodules, interstitial lung disease (ILD), peripheral neuropathy, scleritis/episcleritis, and vasculitis were assessed. Antibody status including rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) titers were also obtained. Other laboratory parameters including hemogram, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin were done as a part of the regular monitoring for patients on DMARD therapy. Past and current therapy of the patients, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, hydroxychloroquine (HCQ), methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF) were also documented.

For evaluation of parasitic infestations, three serial stool examinations were done, considering the episodic nature of parasitic excretion in stool. Serological tests for parasitic infections included qualitative IgG and IgM enzyme-linked immunosorbent assay (ELISA) for *Strongyloides stercoralis*, IgG ELISA for *Taenia solium*, and indirect haemagglutination assay for filariasis and hydatid disease. Patients with an identifiable parasitic infestation were treated accordingly. All patients with eosinophilia in whom a definite cause was not found were treated empirically with albendazole 400 mg twice daily for 3 days. The patients in whom the eosinophilia persisted even after the empirical antihelminthic therapy were evaluated for possible drug-induced eosinophilia. In them, a trial of drug modification was done. Diclofenac sodium was switched to indomethacin, and methotrexate was switched to sulfasalazine in patients wherever it was feasible. The patients on drug modification were regularly monitored for any potential response in eosinophilia with a monthly peripheral eosinophil count, and the modifications were maintained for a minimum period of 3 months. Those patients who had eosinophilia despite the antihelminthic therapy and the drug modification were classified as RA patients with persistent eosinophilia. Demographic parameters and RA-related clinical data were compared between patients with persistent eosinophilia and patients without eosinophilia.

Statistical analysis

For quantitative data, normal distribution was checked by Shapiro–Wilk test. The continuous data were presented as either means ± standard deviation (SD) or median (minimum–maximum/inter-quartile range—IQR 25–75), as appropriate. For data that did not follow a normal distribution, median (IQR 25–75) for the two groups were compared using the Mann–Whitney *U* test. Qualitative or categorical variables were described as proportions. Proportions were tested using Chi-square or Fisher's exact test as appropriate. A p value of < 0.05 was considered significant. Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago) for Windows.

Ethical approval

The study protocol was approved by the institutional ethics committee, and all the study subjects provided written informed consent.

Results

Of the 1092 patients with RA who were screened, 191 patients (17.5%) had eosinophilia. Of these 191 patients with eosinophilia, 31 patients were lost to follow-up. Out of the remaining 160 patients, 37 patients had a definite known cause for eosinophilia, and these patients were also excluded from further investigations. The remaining 123 patients with unexplained eosinophilia were investigated for parasitic infestation, and they completed a minimum period of 1-year follow-up (Fig. 1).

Etiologies of eosinophilia

Of the 160 patients with eosinophilia, 30 patients (19%) had allergic diseases, six patients had bronchiectasis, and one patient had hypereosinophilia of undetermined significance. Intestinal helminthiasis was found in 34 patients (21%). In more than half of the patients (56%, 89 out of 160) the cause of eosinophilia was unexplained.

Intestinal helminthiasis in patients with eosinophilia

Thirty-four patients (21%) out of the 160 had intestinal helminthiasis. Among the intestinal helminthiasis, *Ascaris*

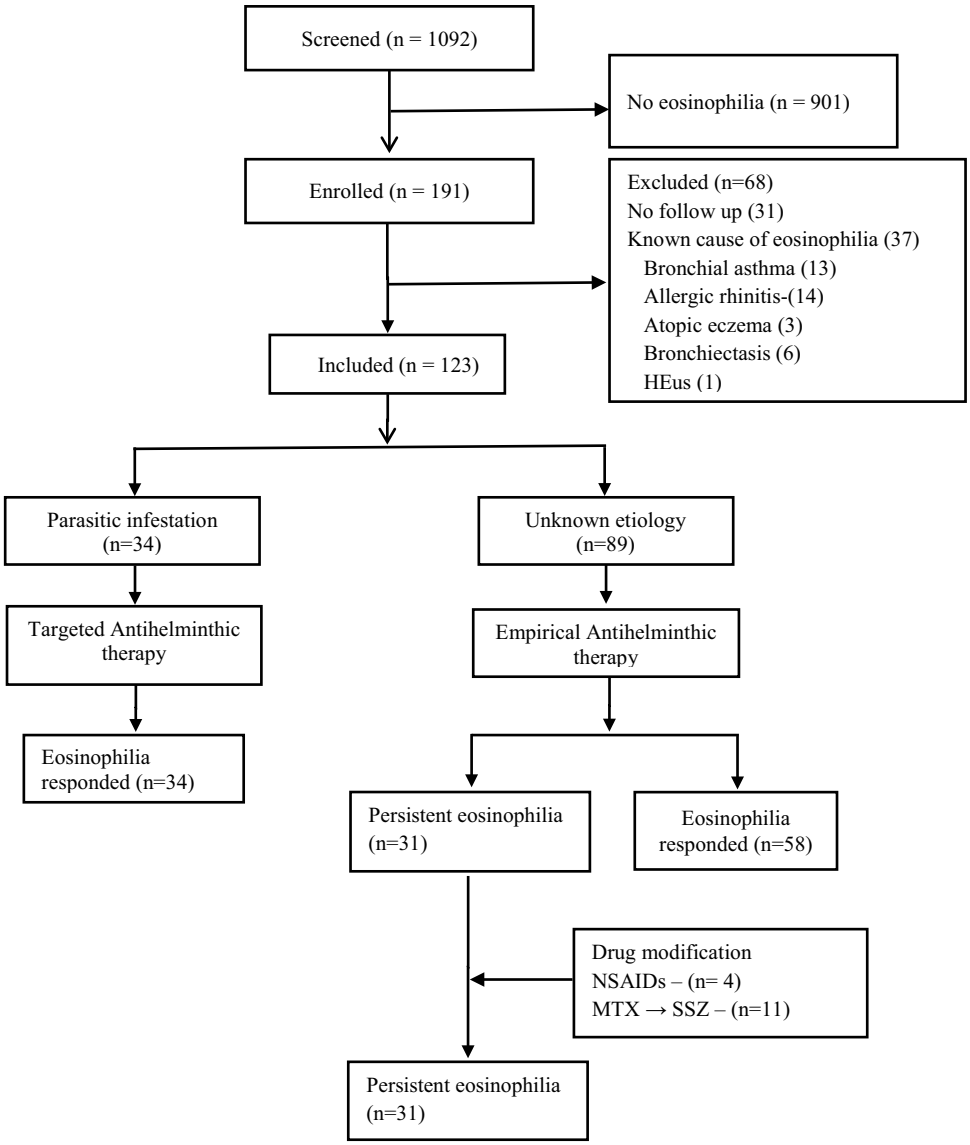

Fig. 1 Disposition of the study participants. HEus, hypereosinophilia of undetermined significance; MTX, Methotrexate; NSAIDs, Nonsteroidal anti-inflammatory drugs; SSZ, Sulfasalazine

lumbricoides infestation was the most common (38%, 13/34) and hookworm was the second most common (29%, 10/34). *Strongyloides stercoralis* infestation was found in six patients, *Hymenolepis nana* and pinworm were identified in two patients each, and one patient had intestinal Taeniasis. The mixed parasitic infestation was also observed in two patients; one had a mixed infection of *Ascaris lumbricoides* and Hookworm and the second patient had mixed infection *Ascaris lumbricoides* and *Strongyloides stercoralis*.

Serology for *Strongyloides stercoralis* (IgG and IgM ELISA) was positive in 11 out of the 123 patients, and among these, two patients also showed positive stool examination result. Out of these 11 patients who had positive IgG ELISA for *Taenia solium*, none showed stool positivity. Serological test for hydatid disease and filariasis was negative in all tested patients. In addition to helminths, stool examination also revealed infection with protozoan parasites. Fifteen patients had protozoans in their stool analysis. Stool examination was positive for *Giardia lamblia* in 4 patients, *Blastocystis hominis* in 6 patients, and *Entamoeba* species in 5 patients.

Allergic diseases and other etiologies in patients with eosinophilia

Thirty patients (19%) out of the 160 had allergic diseases. 14 patients had allergic rhinitis, 13 had bronchial asthma, and 3 had atopic dermatitis. Six patients (4%) had bronchiectasis. One patient had a distinct phenotype of eosinophilia compared to other patients. She had extremely high levels of eosinophilia; her RA was in remission; she did not have any features of allergic diseases, and work up for parasitic infestation was negative. Bone marrow study showed increased eosinophils with no abnormal cells. Analysis of peripheral

blood for Fip1-like 1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA) fusion gene (F/P) and mutation of platelet-derived growth factor receptor beta (PDGFRB) were negative. During the follow-up, she never developed features of end-organ damage. We classified her as hypereosinophilia of undetermined significance (HEus).

Effect of antihelminthic therapy on eosinophilia

In all patients with identifiable helminthic infestations, eosinophilia disappeared after targeted therapy. Among the 89 patients with unexplained eosinophilia, 58 (65%) patients had a resolution of eosinophilia following empiric antihelminthic therapy, and 31 patients (35%) had persisting eosinophilia despite treatment with antihelminthic therapy.

Effect of drugs used for RA on eosinophilia

Of the 31 patients who had persistent eosinophilia despite empirical antihelminthic therapy change of drugs was done in 15 patients. In 4 patients, diclofenac sodium was switched to indomethacin, and in 11 patients, methotrexate was switched to sulfasalazine. Median (IQR) follow-up was 6 (4–6) months following drug modification. None of the patients in whom diclofenac sodium was changed to indomethacin showed any change in eosinophilia pattern. In those patients where methotrexate was switched to sulfasalazine, no response in eosinophilia pattern was observed. In these patients in whom methotrexate was substituted with sulfasalazine, a non-significant increase in median (IQR) DAS28-ESR was seen, 2.58 (2.4–2.74) to 2.74 (1.47–3.5) ($p=0.43$) following drug modification. Similarly, other disease activity measures, tender joints, swollen joints, ESR, VAS for pain and patient-assessed global health and IHAQ did not show any significant change during follow-up. All of the patients were having either low disease activity or remission at the point of drug modification. No patient had features of disease flare during 6 months. However, three of the 11 patients developed disease flares beyond 6 months. Flares happened at 7 months in the first patient, 8 months in the second and 10 months in the third patient.

Comparison between RA patients without eosinophilia versus RA patients with persistent eosinophilia (Table 1)

The age, sex distribution and the median (IQR) disease duration were similar between the two groups. The RF and ACPA titer, the proportion of patients with seropositivity, and the proportion of patients with high RF or ACPA titer were similar between the groups. The proportion of patients having a deforming disease in the persistent eosinophilia group was similar compared to the patients with a normal eosinophil count. The occurrence of sicca, rheumatoid nodule, and ILD was similar in both groups. None of the patients with persistent eosinophilia had features of vasculitis or episcleritis.

Individual and composite measures of disease activity were similar between the two groups. The median (IQR) tender and swollen joint count (TJ28 and SJ28), patient VAS for pain and global health, ESR, and DAS 28 ESR were similar between patients with or without eosinophilia. The functional disability score, IHAQ was also similar between the groups. RA patients with or without eosinophilia were comparable regarding the use of NSAIDs, and steroids. The proportion of patients on individual or combination DMARD therapy was also similar between the two groups.

Discussion

This study prospectively evaluated eosinophilia in RA patients. The prevalence of eosinophilia in RA patients was 17.5%. In the majority, eosinophilia was due to secondary causes, and two-thirds of the patients had either proven intestinal helminthic infection or response to empirical antihelminthic therapy. Modification of DMARDs in patients with asymptomatic eosinophilia led to disease flare. Patient with persistent eosinophilia was comparable to the patient without eosinophilia with respect to disease-related characteristics. These observations may challenge the older concept of associating eosinophilia with severe RA, and are mostly in concordance with the newer studies were such observations were absent.

Studies had shown a different prevalence of eosinophilia in RA, ranging from as low as 3.2% to as high as 21.6%. However, the differences in the definition of eosinophilia, and exclusion criteria used might have affected the reported prevalence in these studies [2–4]. Our population showed a higher prevalence of eosinophilia compared to the Western population. Recently, another study from Kashmir in northern India also reported a similarly high prevalence of eosinophilia in RA patients [4]. The prevalence of eosinophilia in the Indian general population ranges from 8 to 20% and it had been found to be higher in the rural population [20, 21]. This higher population prevalence might have reflected in the RA patients too. The prospective observational design also could have contributed to the higher prevalence, because most previous studies evaluating eosinophilia in RA have been cross-sectional studies [2–4].

In all probabilities two-thirds of our patients harbored an intestinal helminth. This high prevalence of intestinal helminthiasis was not surprising as a high prevalence of intestinal parasites has been reported from this part of the subcontinent [5–7]. A similar study in an Argentinean cohort showed 100% prevalence parasitic infestations in RA

Table 1 RA patients without eosinophilia versus RA patients with persistent eosinophilia

Demographic and clinical characteristics	Non-eosinophilia ($N=901$)	Eosinophilia ($N=31$)	p value[@]
Age (years), median (minimum–maximum)	44 (19–85)	46 (23–65)	0.081[$]
Sex, female, *N* (%)	790 (87.7)	26 (83.9)	0.528[#]
Disease duration (months), median (IQR)	24 (12–60)	24 (7–60)	0.298[$]
Seropositivity, *N* (%)	801 (88.9)	29 (93.5)	0.415[#]
RF (U/ml), median (IQR)	85.5 (17.6–269)	78 (23.2–366)	0.858[$]
RF > 3ULN, *N* (%)	602 (66.8)	22 (71)	0.629[#]
ACPA (U/ml), Median (IQR)	96.6 (13.6–300)	50.5 (15.1–278.8)	0.739[$]
ACPA > 3ULN, *N* (%)	661 (73.4)	23 (77.4)	0.615[#]
Deforming disease, *N* (%)	441 (48.9)	19 (61.3)	0.176[#]
Sicca, *N* (%)	87 (9.7)	3 (9.7)	0.997[#]
Rheumatoid nodules, *N* (%)	51 (5.7)	1 (3.2)	0.561[#]
ILD, *N* (%)	12 (1.3)	1 (3.2)	0.337[#]
Vasculitis, *N* (%)	9 (1)	0	
Episcleritis, *N* (%)	3 (0.3)	0	
NSAIDs, *N* (%)	525 (58.3)	18 (58.1)	0.980[#]
Steroid, *N* (%)	333 (37)	9 (29)	0.368[#]
Hydroxychloroquine, *N* (%)	469 (52)	18 (58.1)	0.510[#]
Methotrexate, *N* (%)	538 (59.7)	23 (74.2)	0.105[#]
Sulfasalazine, *N* (%)	41 (4.6)	3 (9.7)	0.186[#]
Leflunomide, *N* (%)	16 (1.8)	2 (6.5)	0.063[#]
Combination DMARDs, *N* (%)	371 (41.2)	14 (45.2)	0.658[#]
SJ28, median (IQR)	4 (2–6)	4 (2–8)	0.756[$]
TJ28, median (IQR)	8 (4–12)	7 (4–12)	0.783[$]
VAS pain, median (IQR)	40 (20–50)	30 (20–40)	0.174[$]
VAS patient-assessed global health, median (IQR)	40 (20–50)	30 (20–40)	0.139[$]
ESR, median (IQR)	46 (34–61)	54 (35–65)	0.399[$]
DAS 28 ESR, median (IQR)	5.4 (4.5–6.1)	5.27 (4.7–6.1)	0.952[$]
IHAQ, median (IQR)	1.75 (1.42–2.08)	1.67 (1.42–1.92)	0.565[$]

ACPA, Anti-citrullinated peptide antibody; DAS28, Disease Activity Score (28 joints); DMARDs, Disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, interquartile range; IHAQ, Indian version of Health Assessment Questionnaire; ILD, Interstitial lung disease; NSAID, Nonsteroidal anti-inflammatory drugs; RF, rheumatoid factor; SD, standard deviation; SJ28, swollen joint count (28 joints); TJ28, tender joint count (28 joints); VAS, visual analog scale

[@] p values < 0.05 were considered statistically significant

[#] χ^2 test or Fisher's exact test used

[$] Mann–Whitney U test used

patients with eosinophilia, and they observed evidence of parasitic infections in patients without eosinophilia too [2]. This observation was in concordance with a high incidence of parasitic infestation in the geographic region studied [22]. Other than the high prevalence of parasitic infestation in the population studied, the increased risk of infections in RA patients due to disease per se, and also as a consequence of immunosupressive therapy could have also contributed to making them vulnerable to parasitic infestations [8–10]. Such observations were not made in earlier studies or other recent studies, and it is because of two reasons. First, the prevalence of parasitic infestations may vary from region to region. Second, in a few studies, either these were not looked for, or their presence was considered as an exclusion criteria [3, 4, 16].

A significant proportion of our patients also had allergic disorders, an observation similar to in Etude et Suivi des POlyarthrites Indifférenciées Récentes (ESPOIR) cohort [3]. A significant association between common allergic diseases and incident RA was observed in recent studies, and asthma was found to be the second most common comorbidity in patients with RA [23–25]. These observations challenge the general notion that there is an inverse relationship between a type 1 T-helper (Th) cell predominant diseases like RA, and allergic diseases where Th2 cells are the predominant cells in pathogenesis [26, 27]. Th1 and Th 17 are known to

play a vital role in the pathogenesis of RA, and it has also been shown that they are also involved in the inflammatory mechanism of asthma [26, 27]. Studies also have demonstrated that Th2 predominant diseases could coexist with Th1 predominant diseases [28].

Drugs are the most common cause of eosinophilia in regions where parasitic infections are controlled [29]. Diverse therapeutic compounds have been reported to trigger eosinophilic allergic reaction [30]. DMARDs have also been reported to cause drug hypersensitivity reactions, and the manifestations vary from asymptomatic eosinophilia to life-threatening disorders like drug rash with eosinophilia and systemic symptoms (DRESS) [11–15]. The DMARD-induced asymptomatic eosinophilia has been shown to revert back to normal once the offending drug is withdrawn [11, 13, 15]. None of the patient in the study group had any features of drug sensitivity with organ involvement. In a few patients where it seemed feasible, diclofenac sodium was switched to indomethacin, and methotrexate was switched to sulfasalazine and in the rest, the existing treatment was followed. The drug modification trial was done to look for the response in eosinophilia following withdrawal of a particular drug. None of the patients on drug modification showed any change in the eosinophilia; rather a few patients had disease flare after stopping methotrexate. The risk of disease flare with drug modification supports the notion that every drug-induced eosinophilia may not warrant the modification of the drug unless there has occurred a potent complication due to the same [31].

No significant association was seen between persistent eosinophilia and RA-related parameters. Earlier case series by both Winchester and Panush reported an association between high RF titer, severe disease phenotype and some extra-articular features to eosinophilia, but more recent studies did not find any such association [2, 4, 16, 17]. Several factors might have confounded the observations in case series. First, in the Winchester series, there was a bias in selection as patients with severe clinical features, and high titer RF itself were the inclusion criteria [16]. Second, with the advent of early and more targeted oriented treatment strategies, we have succeeded in limiting more severe disease phenotypes in patients [32]. The observations in early arthritis in the ESPOIR cohort differed with our study [3]. The observed discordance could have been primarily because of the difference in study design, which makes the comparison less justifiable. Other recent studied in RA by Chiardola et al. and Sofi et al. did not find any relationship between diseases related factors and eosinophilia in RA [2, 4].

The present study holds its strengths in large sample size, prospective nature of data collection, and a reasonably long enough follow-up to assess the response of eosinophilia. Our study had a few limitations. Even though the prospective observational design helped to gather a larger sample size, it was inadequate to define precisely the temporal relationship between eosinophilia, RA, and the various drug treatments. Only a limited number of investigations were used for evaluating the cause of eosinophilia. More extensive search for parasites with more sensitive and accurate diagnostic techniques could have increased the yield of patients with parasitic infestations. It is possible that the unexplained persistent eosinophilia in few patients was still due to an unidentified parasitic infestation which was not detected in our work up, or was resistant to empirical albendazole therapy. Moreover, the absence of eosinophilia by itself does conclusively prove the absence of parasitic infestation. It might be possible that patients still harbor an unidentified parasitic infection, considering the high prevalence of such infestations, and the chance of mixed infections. The diagnoses of allergic diseases were entirely based on the clinical details, and it is possible that patients with the suspected allergic disease had a coexisting parasitic infestation. Exclusion of these patients from the analysis might have affected the results. Considering the role of therapeutic agents in inducing eosinophilia, it was a limitation that none of the patients in the study were on biologic DMARD therapy, however, this is primarily because most patients in this setting are unable to afford biologic DMARDs [33].

In conclusion, a considerable proportion of RA patients had eosinophilia, and it was mostly due to secondary causes, intestinal helminthiasis being the most common cause. In the RA patient with eosinophilia, a detailed search for intestinal helminths should be done, and empirical therapy with an antihelminthic drug may be justifiable, particularly in the Indian population or other similar regions, where the prevalence and risk of intestinal helminthic infestation are high. In unexplained eosinophilia, if there is no overt manifestation of organ involvement due to drug hypersensitivity, drug modification does not seem to be warranted. The presence of persistent eosinophilia in our patients with RA did not portend a more severe disease phenotype. The exact temporal relationship between eosinophilia and RA needs further exploration in longer-term studies.

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Author contributions (1) The conception and design of the study—DE, SCP, RK, and VSN. Acquisition of data—DE, SCP, AJ, and DPM. Analysis and interpretation of data—DE, SCP, AJ, and DPM. (2) Drafting the article—DE, AJ, and DPM. Revising it critically for important intellectual content—SCP, RK, and VSN. (3) Final approval of the version to be submitted—DE, SCP, AJ, DPM, RK, and VSN. (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved—DE, SCP, AJ, DPM, RK, and VSN.

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Compliance with ethical standards

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approved by the Institute Ethics Committee of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, held on 11th December 2014 (JIP/IEC/2014/10/480).

Conflict of interest Dantis Emmanuel declares that he has no conflict of interest. Subhash Chandra Parija declares that he has no conflict of interest. Ankit Jain declares that he has no conflict of interest. Durga Prasanna Misra declares that he has no conflict of interest. Rakhee Kar declares that she has no conflict of interest. Vir Singh Negi declares that he has no conflict of interest.

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