Subacute Prurigo and Eosinophilia in a Patient With Rheumatoid Arthritis Receiving Infliximab and Etanercept

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Palabras clave: Eosinofilia. Infliximab. Etanercept.

An 80-year-old woman diagnosed with rheumatoid arthritis 22 years ago and with no other relevant medical or allergic conditions had been treated with methotrexate and prednisone for 2 years with good control of disease activity. In January 2007, methotrexate was stopped due to marked leukopenia, and treatment with intravenous infliximab was started at a dose of 3 mg/kg every 2 weeks, with an adequate clinical response and tolerance.

In April 2007, she developed a clinical picture consisting of intense and widespread itching associated with papules and vesicles over a slightly erythematous base. We also observed that she had been scratching her lesions. Blood tests and a differential white blood cell count revealed eosinophilia (720 eosinophils/mm^3). A skin biopsy performed at the dermatology department showed severe dermal swelling with a lymphocytic infiltrate and abundant perivascular eosinophils. The diagnosis was subacute prurigo with eosinophilia. The suspicion of a probable adverse drug reaction led us to discontinue infliximab and prescribe topical and systemic treatment with corticosteroids. The skin lesions disappeared completely and eosinophil values returned to normal within 4 months (Figure).

As her rheumatoid arthritis was partially controlled with systemic corticosteroids, her rheumatologist initiated treatment with intravenous etanercept at 25 mg twice a week in August 2008. However, the skin lesions reappeared for 1 month. Eosinophilia increased to 1020 eosinophils/mm^3 (Figure). Etanercept was withheld and methylprednisolone (60 mg/d) was started until the clinical picture subsided (1 month later). Skin prick tests and patch tests were performed with infliximab (100 mg/mL) and etanercept (25 mg/mL) and yielded negative results. The patient was diagnosed with subacute prurigo and eosinophilia induced by infliximab and etanercept.

Prurigo is a condition involving nodular cutaneous lesions that itch intensely. Although the acute form can be caused by insect stings, most subacute and chronic forms appear to be idiopathic. Toxic agents deposited on the skin by exogenous factors such as parasites, bacteria, or topically or orally administered drugs can induce itching [1].

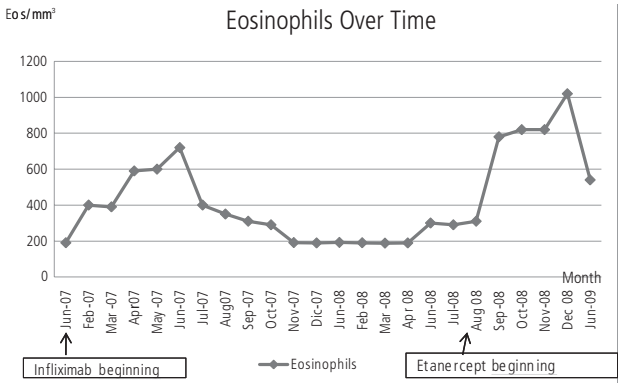

Figure. Eosinophil count over time.

The key aspect for diagnosis in this unique case of subacute prurigo was a comprehensive clinical history and the temporal relationship between administration and the development of cutaneous lesions and systemic eosinophilia, which is an important marker of drug reactions.

Tumor necrosis factor (TNF) α inhibitors are increasingly used in the treatment of autoimmune diseases and have a relatively favorable safety profile. However, several side effects, some of which are severe, have been reported [2]. Those consistent with immunosuppression include severe infections (tuberculosis), increased risk of lymphoma and solid tumors, and the development of the antinuclear autoantibodies responsible for lupus. Adverse dermatological reactions with TNF-α inhibitors at the injection site are common and usually self-limiting. Other skin reactions include erythema nodosum and cutaneous vasculitis [3]. However, to the best of our knowledge subacute prurigo or systemic eosinophilia associated with etanercept or infliximab have not been previously reported among the side effects of TNF-α inhibitors in patients with rheumatic diseases. Winfield and Edward [4] reported a case of eosinophilic cellulitis-like reaction due to subcutaneous etanercept in a patient with rheumatoid arthritis, although they made no reference to systemic eosinophilia.

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Inflammatory Phenotypes in Nonsmoking Asthmatic Patients

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Palabras clave: Asma bronquial. Eosinofilia. Esputo inducido. Fenotipo inflamatorio.

Bronchial asthma is a heterogeneous disease in which several clinical, functional, and inflammatory phenotypes have been described. Induced sputum analysis has revealed 4 subtypes of inflammatory phenotypes—eosinophilic, neutrophilic, paucigranulocytic, and mixed cellularity—depending on the presence or absence of eosinophils and/or neutrophils in sputum [1]. Eosinophilic asthma has been linked to allergy and immunoglobulin (Ig) E–mediated eosinophilic inflammation and is considered to be the most frequent subtype, although wide differences in prevalence (22% to 88%) have been reported [2]. Neutrophilic inflammation has been demonstrated in persistent and severe asthma and in acute exacerbations. Smoking and inhaled corticosteroids may also lead to increased sputum neutrophilia [3]. The aim of our study was to assess the prevalence of the different inflammatory phenotypes in a large sample of nonsmoking asthmatic patients and compare the clinical and functional characteristics of the different groups formed according to the inflammatory phenotype.

Our sample comprised 147 clinically stable nonsmoking asthmatic patients referred to a secondary care allergy center. Asthma was diagnosed according to current guidelines [4]. The exclusion criteria were respiratory infection in the preceding 4 weeks, use of oral prednisolone in the previous 3 months, other pulmonary disease, and significant comorbidity. Sputum induction and cytological analysis of the whole sputum sample were performed according to Fahy et al [5]. Inflammatory phenotypes were defined using cutoffs of ≥/<2% for sputum eosinophils and ≥/<61% for sputum neutrophils [6]. In addition to clinical and demographic characteristics, we measured fractional exhaled nitric oxide (FE_{NO}) (Aerocrine Niox Minor, Aerocrine AB, Solna, Sweden), spirometry, and bronchial reactivity to hypertonic saline. Bronchial reactivity was assessed according to a standardized protocol and the results were expressed as the dose-response slope [7]. All patients gave their written informed consent to participate. All procedures were performed according to the principles of Good Clinical Practice and for clinical reasons that are generally part of routine follow-up or to confirm the diagnosis.

Adequate sputum samples were obtained in 117 patients (80%). Median age was 19 years (range, 8 to 75), 51% were female, and 79% were atopic, defined as a positive response to at least 1 inhalant allergen. The main results are presented in the Table. Panel A shows the frequency of the phenotypes for the whole sample and for the 2 groups based on whether patients were treated with inhaled corticosteroids or not. Eosinophilic asthma was by far the most prevalent phenotype, followed with a similar frequency by the paucigranulocytic and mixed phenotypes. Only 2 patients were classified as neutrophilic. Both were nonatopic and on treatment with inhaled corticosteroids. Because of this low number, we did not proceed to further comparisons with this group. Phenotypes were not different in terms of age, gender, or presence of atopy. The eosinophilic and mixed phenotypes had a lower ratio of

Table. Phenotype Frequencies and Functional Characteristics[a]

A. Phenotype Frequencies

Phenotype/ Group	All Samples	Salbutamol As Needed	Inhaled Corticosteroid
N	117	79	38
Paucigranulocytic	25 (21%)	18 (23%)	7 (18%)
Eosinophilic	69 (59%)	49 (62%)	20 (53%)
Neutrophilic	2	0	2

B. Functional Characteristics

Phenotype/ Outcome	Nonatopic	FEV_1/FVC	Hypertonic Dose-Response Slope	FE_{NO} ppb
Paucigranulocytic	4 (16%)	85 (80-86)	0.46 (0.12-3.00)	23 (19-33)
Eosinophilic	12 (17%)	75 (71-80)[b]	2.4 (0.58-7.7)[b]	47 (31-37)[b]
Neutrophilic	2	62	1.2	27
Mixed	7 (33%)	78(72-84)[b]	2.6 (0.64-8.3)[b]	67 (33-100)[b]

Abbreviations: FE_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volumen in the first second; FVC, forced vital capacity.
[a]Figures are presented as absolute numbers and percentages and as the median (interquartile range).
[b]P<.01 compared to the paucigranulocytic phenotype.

forced expiratory volume in the first second to forced vital capacity (Kruskal-Wallis, *P*<.003) than the paucigranulocytic phenotype, were more reactive to hypertonic saline (Kruskal-Wallis, P<.023), and had higher levels of FE_{NO} (Kruskal-Wallis, *P*<.001), as shown in panel B. Results and differences between phenotypes for patients not treated with inhaled corticosteroids were of a similar magnitude: FE_{NO} was 20 ppb (19-33) for the paucigranulocytic phenotype, 45 ppb (34-71) for the eosinophilic phenotype, and 62 ppb (33-126) for the mixed phenotype; the hypertonic saline dose response slope revealed 0.46 (0.17-1.49) for the paucigranulocytic phenotype, 2.38 (0.58-8.75) for the eosinophilic phenotype, and 1.22 (0.64-7.33) for the mixed phenotype. Porsjberg et al [8] had previously shown that eosinophilic asthma had higher levels of reactivity to mannitol than the paucigranulocytic or neutrophilic phenotypes.

In conclusion, we found that the eosinophilic phenotype was the most prevalent inflammatory phenotype in patients treated or not treated with inhaled corticosteroids. Cellularity was linked to functional characteristics. Eosinophilic or mixed phenotypes presented higher levels of bronchial obstruction and were more reactive than the paucigranulocytic phenotype. Neutrophilic asthma was extremely infrequent and, as it was observed in only 2 treated patients, we can hypothesize that inhaled corticosteroids could play a role.

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Drug Fever Caused by Piperacillin-Tazobactam

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Key words: Adverse drug reaction. Drug hypersensitivity. Piperacillin-tazobactam.

Palabras clave: Reacción adversa a medicamentos. Hipersensibilidad a medicamentos. Piperacilina-Tazobactam.

Drug fever is frequently misdiagnosed, because physicians generally associate fever with an infectious disorder.

A drug can cause fever by different mechanisms, including exogenous pyrogenicity, alteration of central temperature regulation, pharmacologic action, idiosyncratic reactions, and hypersensitivity mechanisms [1].

The median time between initiation of the causal agent and onset of fever ranges from 7 to 10 days [2]. After discontinuation of the drug, fever generally resolves within 48-72 hours, although it may persist for weeks if there are other manifestations, such as maculopapular rash, or if the elimination rate of the agent is low [3]. A major problem with drug fever is that the reaction may become more generalized and cause tissue damage [4]. Cutaneous manifestations are observed in 18%-29% of patients [5] and tend to support the diagnosis [4]. Rechallenge with the offending agent usually causes recurrence of fever within a few hours, thus confirming the diagnosis [3].

A 65-year-old man was admitted to our hospital because of chronic infection in his Achilles tendon. The patient started treatment with piperacillin-tazobactam and 13 days later developed intense shivering with fever (39ºC) and a widespread rash with erythema and wheals with pruritus. Treatment with piperacillin-tazobactam was discontinued. Although no infectious signs were observed in the tendon, meropenem was added to complete the treatment. The microbiologic analyses of blood and injury exudates were both negative. Forty-eight hours after onset of fever, the patient's temperature returned to normal. Because the rash persisted for a further 2 days, meropenem was stopped and tigecycline started. The patient continued this treatment during the next 4 weeks, with good tolerance, and the rash disappeared.

After obtaining written informed consent, we performed diagnostic studies according to the recommendations of the European Network for Drug Allergy for diagnosis of immediate allergic reactions to ß-lactams [6]. Skin tests were carried out with penicilloyl-polylysine, minor determinant mixture, benzylpenicillin (penicillin G), amoxicillin, ampicillin, cefuroxime, piperacillin-tazobactam, and meropenem. The prick and intradermal tests were negative with all of the reagents. Single-blind controlled intramuscular challenge with increasing doses of piperacillin-tazobactam to a dose of 500 mg was immediately negative. Six hours later, the patient developed shivering, mild erythema, and fever (39ºC). He was given intramuscular corticosteroids, antihistamines, and oral

paracetamol in the emergency room. Symptoms resolved 1 hour later. During the next few days, the patient did not have fever or any symptoms that suggested infection. Single-blind controlled intramuscular challenge with increasing doses of meropenem to 500 mg and oral challenge with amoxicillin to 500 mg were both negative.

We present a case of drug fever that was not initially suspected and in which the patient was studied following the protocol for penicillin allergy.

Due to the presence of cutaneous manifestations and because the fever recurred within 6 hours after rechallenge, the patient was diagnosed with drug fever caused by piperacillin-tazobactam, and a hypersensitivity mechanism was suspected.

As the patient could need ß-lactam antibiotics in the future, we recommended avoiding piperacillin-tazobactam, although he tolerated penicillin-unrelated substitutes (meropenem and amoxicillin).

A recent review showed that antibiotics, particularly ß-lactams, are increasingly associated with a higher incidence of drug fever [1].

Drug fever is usually diagnosed by exclusion after elimination of other potential causes. We would like to encourage physicians to be aware of this entity. Prompt identification can obviate unnecessary diagnostic procedures and inappropriate treatment [4].

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Occupational Asthma Induced by *Mucor* Species Contaminating Esparto Fibers

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Palabras clave: Asma ocupacional. *Mucor* species. Esparto

Esparto grass is a member of the Poaceae family that is found throughout the Mediterranean region. It has several applications in industry, particularly in the manufacture of ropes, hemp sandals, rush mats, and baskets. It is also used for decorative purposes in the building industry to attach stucco plates to walls and ceilings. During the manufacturing process, the fibers may become contaminated with moulds. Workers exposed to esparto fibers may develop hypersensitivity pneumonitis or asthma [1-4].

We report the case of a 30-year-old man (smoker) who worked as a stucco maker in the building industry and who had been exposed to esparto fibers for 12 years. He presented with a 3-year history of cough, shortness of breath, and wheeze after exposure to esparto fibers. The patient reported daily symptoms that worsened immediately after handling the fibers and persisted for 6-8 hours. His condition improved when he was outside work and during vacations and weekends. He had no fever or other systemic symptoms suggesting hypersensitivity pneumonitis. A blood test showed eosinophilia (0.64×1000/μL) and his chest radiograph was normal. Skin prick tests (SPT) carried out with an in-house extract of esparto fibers (10% w/v) provided by the patient elicited a positive result (4 mm). SPT with a standard battery of common aeroallergens including pollens, dust mites, epithelia, and moulds (*Aspergillus, Alternaria*, and *Cladosporium*) were negative. Total serum immunoglobulin (Ig) E (CAP-System FEIA, Phadia) was 459 kU_A/L. Specific serum IgE against *Aspergillus fumigatus* was negative (CAP-System FEIA). Spirometry was normal and the methacholine challenge test result was positive. The peak expiratory flow measurements taken at work and outside work showed a decrease in respiratory function at work, suggesting an occupational relationship, although 20% variability was not reached. The sample provided by the patient was cultured for moulds and *Mucor* species were detected. No other mould species were identified. The result of subsequent SPT with *Mucor* extract (ALK-Abelló, Madrid, Spain) was positive (7 mm). Specific serum IgE against *Mucor racemosus* was detected (1.98 kU_A/L) (CAP-System FEIA).

After signing an informed consent form, the patient underwent controlled exposure with esparto fibers tipped from one tray to another while spirometry was monitored as proposed by Pepys and Hutchcroft [5]. In the first 5 minutes, the patient presented with rhinitis and asthma symptoms with a 43% fall in forced expiratory volume in the first second of

expiration (FEV_1). The patient was treated immediately with corticosteroids and bronchodilators. No late reaction was observed. A specific bronchial challenge with *Mucor* extract (ALK-Abelló) elicited an immediate asthmatic reaction (15% fall in FEV_1). The patient has been symptom-free since changing his job.

Several cases of hypersensitivity pneumonitis caused by esparto inhalation have been reported, and these were caused mainly by moulds such as *A fumigatus* [1] or, less frequently, by *Mucor* [2]. Only 2 cases of asthma caused by esparto dust [3] and esparto contaminated by *A fumigatus* [4] have been reported.

To our knowledge, this is the first case of occupational asthma induced by *Mucor* species contaminating esparto fibers.

A thorough study of possible mould sensitization should be carried out in patients reporting respiratory symptoms induced by esparto fibers in the workplace. Moulds present in cultured samples of esparto fibers could reveal the culprit.

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