

RESEARCH ARTICLE

Hypereosinophilia: Biological investigations and etiologies in a French metropolitan university hospital, and proposed approach for diagnostic evaluation

Martin Peju^{1,2}, Alban Deroux³, Hervé Pelloux^{2,4}, Laurence Bouillet³, Olivier Epaulard^{1,2*}

1 Infectious Diseases Unit, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France, **2** Fédération d'infectiologie multidisciplinaire de l'arc alpin, Université Grenoble Alpes, Grenoble, France, **3** Internal Medicine Unit, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France, **4** Parasitology-Myology laboratory, Centre Hospitalier Universitaire Grenoble Alpes and University Grenoble Alpes, Grenoble, France

* OEPaulard@chu-grenoble.fr



OPEN ACCESS

Citation: Peju M, Deroux A, Pelloux H, Bouillet L, Epaulard O (2018) Hypereosinophilia: Biological investigations and etiologies in a French metropolitan university hospital, and proposed approach for diagnostic evaluation. PLoS ONE 13 (9): e0204468. <https://doi.org/10.1371/journal.pone.0204468>

Editor: Mark Simonds Riddle, Uniformed Services University of the Health Sciences, UNITED STATES

Received: July 30, 2018

Accepted: September 8, 2018

Published: September 26, 2018

Copyright: © 2018 Peju et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data are already available at www.osf.io/7bkn9/.

Funding: The author received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Objectives

We aimed to evaluate the usefulness of biological investigations in cases of eosinophilia in our area (French Alps).

Methods

We retrospectively included all adult patients attending the infectious disease and internal medicine units between 2009 and 2015 with eosinophilia ≥ 1 G/l.

Results

We identified 298 cases (129 women and 169 men). In 139 patients, eosinophilia had not been addressed. In the 159 others, the cause of eosinophilia was identified in 118 (74.2%). The main identified causes at the time were drug reactions (24.5%, mostly β -lactams and allopurinol), infectious diseases (17.0%), vasculitis (8.2%), autoimmune diseases (6.9%), and malignant diseases (6.2%). In patients with a skin rash, eosinophilia was significantly more often investigated, and a diagnosis significantly more often made. Helminthosis were mainly diagnosed in tropical travelers (18/24) excepting toxocarasis (3 non-travelers). Stool examination for helminthosis was positive in 5/76 patients (6.6%) (all tropical travelers); 391 helminth serologies were performed in 91 patients, with 7.9% being positive (all but 3 positive cases were travelers). Anti-neutrophil cytoplasmic antibodies (ANCA) were positive in 26/112 patients (23.2%), with 9 cases of vasculitis identified.

Conclusions

Drug-related eosinophilia is the main etiology. Search for helminthosis is not recommended among non-travelers (excepting toxocarasis). ANCA should be performed early so as not to overlook vasculitis.

Introduction

Blood eosinophilia is defined as a level of eosinophilic granulocytes above 0.4 or 0.5 G/l (1 G/l = 10^9 cells per liter) on the blood count; the levels of blood eosinophilia may be described as mild (0.5–1.5 G/l), moderate (1.5–5 G/l), or severe (>5 G/l) [1]. Eosinophils are key effectors of innate immunity against helminth parasites and as part of the allergic inflammation. After being produced in bone marrow, they circulate for only a few hours before being recruited in tissue where they act in diverse ways: degranulation (sudden release of the highly reactive content of their granules), cytokine production, and phagocytosis; blood eosinophilia is not strictly correlated with tissue infiltration by these cells. The incidence of eosinophilia can dramatically change depending on the world region or the existence of a recent travel history. In large transversal studies of routine medical samples, blood eosinophilia has been estimated to affect 0.4 to 4% of all blood counts [2,3], whereas it has been found in 4 to 27% of returning travelers or arriving refugees [4,5]. When eosinophilia is present, the suspected diagnoses may vary depending on the conditions: for example, in returning travelers, 18.9 to 53.7% of eosinophilia cases are related to an helminth infection [4,6]. However, eosinophilia is associated with a broad variety of non-helminth diseases (including hematological malignancy, vasculitis, allergic diseases, and hypereosinophilic syndrome). Because of this diversity, the diagnostic approach may become complex. Several authors have reviewed the diagnoses associated with blood eosinophilia [7–11], although the diagnostic strategy, which is strongly dependent on the clinical condition and circumstances, is less often detailed. Indeed, recommended examinations may differ from one publication to another.

We therefore aimed to detail in a retrospective study the etiologies of eosinophilia in Grenoble University Hospital (French Alps) and determine which laboratory tests are profitable in this context.

Materials and methods

All patients with an eosinophilia ≥ 1 G/L who attended the internal medicine or infectious disease units of Grenoble University Hospital between 2009 and 2015 were included. The subjects may have consulted or been hospitalized. We choose this threshold (1 G/L) by assuming that a high proportion of cases of eosinophilia between 0.5 and 1 G/L might have been overlooked by clinicians.

Clinical and biological data were collected. All elevated values of aspartate transaminase and/or alanine transaminase (i.e., at least twice the upper normal value) during the period of eosinophilia were considered to be “cytolysis.” Elevated alkaline phosphatase and/or gamma glutamyl-transferase (same) were considered to be “cholestasis.” The diagnosis confirmed at the time by the medical team was retrieved from the medical records.

Chi-square and Fischer tests were used for intergroup comparisons of categorical variables for groups of more or less than 20 patients, respectively. Student's t-test was used for quantitative variables. P-values <0.05 were considered to be statistically significant.

Study ethics approval was obtained from the *Comité d'Ethique des Centre d'Investigation Clinique de la Région Auvergne Rhône-Alpes* (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891); patient consent for chart review was exempted.

Results

Eosinophil count and population

The population was composed of 129 women and 169 men, with a median age of 66 [25th percentile = 47; 75th percentile = 80; range 13–99] (Fig 1). The mean maximal eosinophilia was

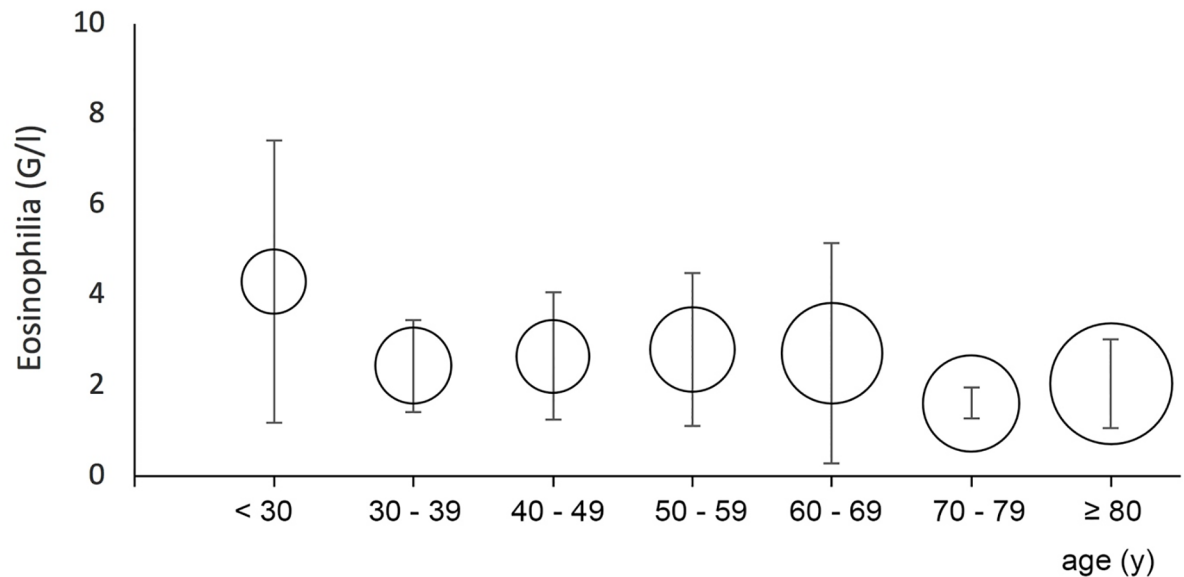


Fig 1. Mean eosinophilia and age. Bars indicate standard derivations around the mean. The center of each circle is placed to the mean eosinophilia of the corresponding age group. The surface of the circles is proportional to the number of patients in the corresponding age group.

<https://doi.org/10.1371/journal.pone.0204468.g001>

2.46 ± 1.7 G/L (median 1.6 G/L; 25th percentile = 1.1; 75th percentile = 2.3). There was no significant difference between men and women with respect to their age and value of their maximal eosinophilia.

Etiologies of eosinophilia

Etiologies of eosinophilia are summarized in Table 1. The existence of eosinophilia was not taken into account in 139 (46.6%) of the 298 selected cases. This proportion was higher for mild eosinophilias (92 of 153 cases [60.1%] with an eosinophilia <1.5 G/L; 46 of 120 cases [38.3%] with an eosinophilia between 1.5 and 5 G/L; and 1 of 25 cases [4.0%] with an eosinophilia >5 G/L, $p < 0.01$). The cause of eosinophilia was identified in 118 cases (74.2% of the 159 explored cases, and 39.6% of the entire population). In 41 patients, the eosinophilia was explored or mentioned in the medical records, but without diagnosis.

Drug-related eosinophilia. The most frequently identified cause of eosinophilia was a drug reaction: 39 patients (13.1% of the entire population, and 24.5% of the population whose eosinophilia was taken into account) received this diagnosis, including 10 with a diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS); 60.0% of patients with DRESS had a fever. Allopurinol alone was involved in six cases of eosinophilia, including three DRESS. Antibiotics were also well represented: a beta-lactam-induced eosinophilia was identified for 14 patients (4.7% of the whole population) (piperacillin/tazobactam in four cases and amoxicillin in three cases), while trimethoprim/sulfamethoxazole was involved in three cases. Incriminated molecules are listed in Table 2. For two patients, a drug reaction was identified despite no causative agent being identified. Globally, patients with drug-related eosinophilia were significantly older (mean age 70.4 ± 8 vs 61.1 ± 10 , $p < 0.05$).

Infectious diseases. A diagnosis of infection was observed for 17.0% (27 of the 159 patients whose eosinophilia was taken into account). Among the 24 cases of helminth infection as the source of eosinophilia (Table 3), 17 were biologically proven, whereas it was only suspected for seven on the basis of a suggestive clinical context (including four tropical/

Table 1. Diagnosis of cases of eosinophilia above 1 G/l in whom diagnostic evaluation was performed (N = 159).

Etiologies	N (%)
No cause identified	41 (25.8)
Hematologic malignancies	5 (3.1)
Iatrogenic reaction	39 (24.5)
DRESS (drug reaction with eosinophilia and systemic symptoms)	10 (6.3)
Others	29 (18.2)
Infections	27 (17.0)
Helminth infections (certain diagnosis)	15 (9.4)
Helminth infections (successful presumptive treatment)	7 (4.4)
Other parasitic (protozoan) diseases (giardiasis, amoebiasis, scabies)	3 (1.9)
Bacterial infections	2 (1.3)
Allergies and atopia	7 (4.4)
Asthma	4 (2.5)
Atopic dermatitis, food allergy	3 (1.9)
Vasculitis	13 (8.2)
Eosinophilic granulomatosis with polyangiitis	6 (3.8)
Granulomatosis with polyangiitis	5 (3.1)
Microscopic polyangiitis	2 (1.3)
Other autoimmune diseases	11 (6.9)
Bullous pemphigoid	2 (1.3)
Dermatopolymyositis	1 (0.6)
Polymyalgia rheumatica	1 (0.6)
Inflammatory bowel disease	1 (0.6)
Inappropriate IL-5 production by tumor cells	5 (3.1)
Eosinophilic infiltration of isolated organs	6 (3.8)
Hypereosinophilic syndrome	5 (3.1)

<https://doi.org/10.1371/journal.pone.0204468.t001>

subtropical travelers) and the success of empirical treatment. Identified parasites were mostly tropical (including four with schistosomiasis), although three *Toxocara canis* infections were found. A non-helminth infection was identified in three cases.

Others. Eosinophilia was attributed to vasculitis for 13 patients (4.4% of the whole population) and autoimmune disease for 11 patients (3.7%). A hypereosinophilic syndrome was diagnosed in five cases and a solid tumor IL-5 expression in five cases. An isolated organ eosinophilic infiltration was detected in six patients.

Severe eosinophilia

Overall, 25 patients had a maximal eosinophilia ≥ 5 G/l, of which 24 cases were explored. The examinations performed led to the diagnoses of infectious disease (three cases), hematological malignancy (four cases), and vasculitis (four cases).

Associated conditions

A total of 141 patients (47.3%) had a fever during eosinophilia, 78 a skin rash (26.2%), 70 digestive symptoms (23.5%), 71 liver cytolysis (23.8%), and 112 cholestasis (37.6%). Recent travel to a tropical region was reported by 40 patients.

Travel. Among the 40 tropical travelers, helminth infections were the most commonly identified cause of eosinophilia (18 cases, 45.0% of travelers). The period between the travel and the first reported eosinophilia was less or more than a year for 21 patients and eight

Table 2. Incriminated drugs.

Molecule		Drug reaction	DRESS	Total
Xanthine oxidase inhibitor		Allopurinol	3	3
Antibiotics	β-lactamins	Cloxacillin	1	0
		Amoxicillin	1	2
		Amoxicillin/clavulanate	2	0
		Piperacillin/tazobactam	3	1
		Ertapenem	2	0
		Ceftriaxone	2	0
		Moxifloxacin	2	0
		Trimethoprim/sulfamethoxazole	2	1
		Anti-tuberculosis	1	1
		Antifungals	Voriconazol	1
Monoclonal antibodies	Adalimumab	1	0	
	Tocilizumab	1	0	
Anti-inflammatories	Diclofenac	1	0	
	Sulfasalazine	0	1	
Anti-epileptics	Carbamazepine	1	1	
Beta-blockers	Bisoprolol	1	0	
Selective serotonin reuptake inhibitors	Sertraline	1	0	
Proton-pump inhibitors	Pantoprazole	1	0	
Other	Hyaluronic acid	1	0	
Unknown medication			2	0
Total		30*	10	40*

*A total of 40 drugs were identified as the cause of eosinophilia, with 39 patients being concerned by a drug reaction. For one of them, two distinct eosinophilic reactions were identified, with two different successive medications.

<https://doi.org/10.1371/journal.pone.0204468.t002>

patients, respectively, and unknown for 11. Destinations where helminth infections were acquired are listed in Table 3.

Skin rash. Overall, 78 patients had a skin rash during eosinophilia (26.2% of the whole population [78 out of 298]). When it was accompanied by a skin rash, the eosinophilia was significantly more often taken into account (63 out of 78 patients with skin rash [80.8%] vs 96 out

Table 3. Parasites and country of infestation.

Parasite	Number of cases	Destination
<i>Ancylostoma</i>	1	Indonesia (Bali)
<i>Ascaris lumbricoides</i>	1	Morocco
<i>Dientamoeba histolytica</i>	1	French Guiana
<i>Fasciola hepatica</i>	1	Cabo Verde
<i>Giardia intestinalis</i>	1	Central African Republic
<i>Gnathostoma sp</i>	1	China
<i>Mansonella perstans</i>	1	Gabon
<i>Onchocerca volvulus</i>	1	Gabon
<i>Schistosoma sp</i>	4	Central African Republic (2 patients), Burkina Faso, Ouganda
<i>Strongyloides stercoralis</i>	2	Guadeloupe, Senegal
<i>Toxocara canis</i>	3	No travel

<https://doi.org/10.1371/journal.pone.0204468.t003>

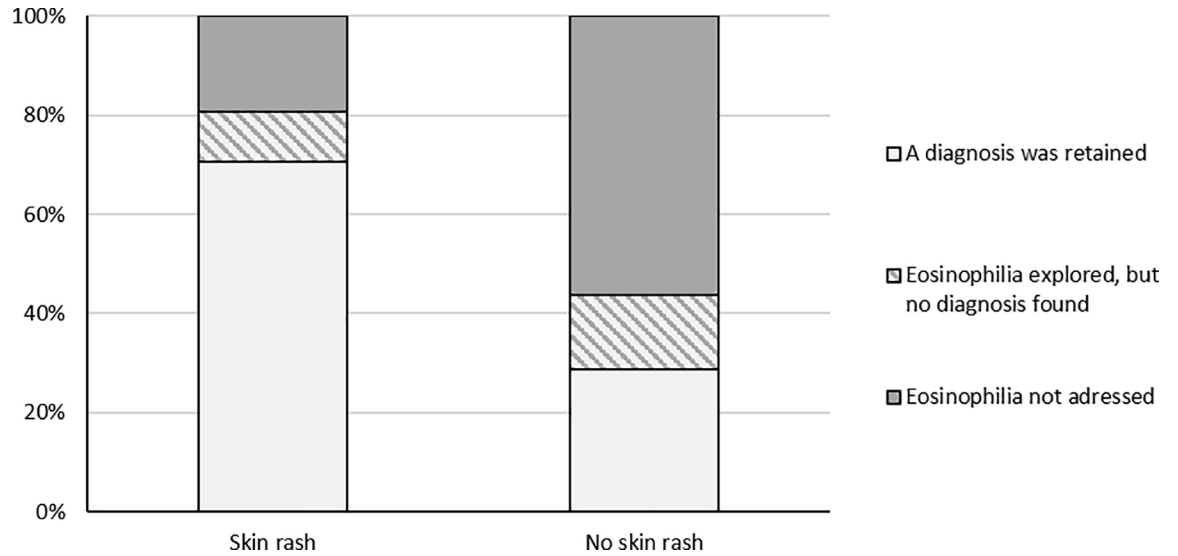


Fig 2. Influence of the presence of a skin rash on the diagnostic process (patients with a skin rash (N = 78) or without a skin rash (N = 220)).

<https://doi.org/10.1371/journal.pone.0204468.g002>

of the 220 without [43.6%], $p < 0.001$), and a diagnosis was then more often made (55 out of 63 patients with a skin rash [87.3%] vs 63 out of 96 without [65.6%], $p < 0.01$) (Fig 2). The most frequent diagnosis was drug-related eosinophilia for these patients (27 out of 63 patients with a skin rash [42.9%] vs 12 out of 96 without [12.5%], $p < 0.001$) (Fig 3).

Fever. A total of 141 patients presented with fever. Notably, 56.4% of drug reactions (including 60.0% of DRESS cases) had a body temperature $> 38.5^{\circ}\text{C}$. When explored, the cases

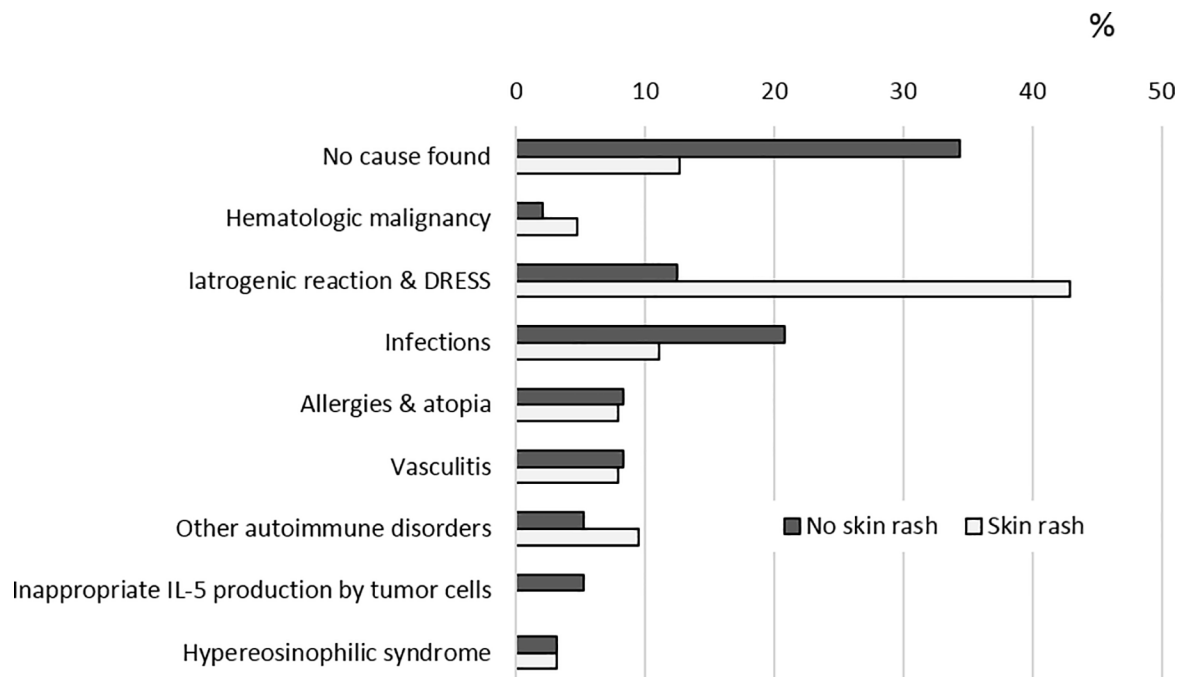


Fig 3. Confirmed diagnosis in patients with a skin rash (N = 63) or without a skin rash (N = 96) (in patients whose eosinophilia was explored).

<https://doi.org/10.1371/journal.pone.0204468.g003>

with both eosinophilia and fever received a diagnosis of drug reaction in 29.7% of patients, and a diagnosis of infectious diseases in 10.8%.

Digestive symptoms. Digestive symptoms were observed in 70 patients; 11 had a diagnosis of helminth infection, of whom 9 had a recent travel history.

Laboratory tests

Stool examination. A stool examination was performed in 76 cases (25.5%). One or two (negative) stool sample(s) were collected from 46 patients, i.e., under the recommended number of three stool examinations. For 25 other patients, this examination was performed three times without identifying a parasite. For five more patients, a stool examination was positive; all five patients had returned from a tropical country. Among the 222 patients who did not have a stool examination, three received a diagnosis of helminthosis, with one case each of schistosomiasis, onchocerciasis, and toxocariasis.

Serologies. A total of 391 helminth serologies was performed in 91 patients (including 173 serologies in 30 travelers). *Toxocara* serology was the most frequently used (72 times). Overall, 31 serologies were positive in 20 patients (seven had two or more positive serologies). Among the 31 positive results, 11 (35.4%) led to a diagnosis of parasitosis in 11 cases (eight travelers and three cases of toxocariasis). For two other patients, parasitosis was detected by other means.

Immunoglobulin E. Total immunoglobulin E (IgE) was determined in 51 patients. Elevated IgE levels (>150 UI/ml) were found in 24 cases. This condition was not specific, as it was associated with helminth infection (six cases), allergic diseases (four cases), and vasculitis (five cases).

Discussion

In our center, etiologies associated with an eosinophilia were dominated by drug reactions and helminth diseases. Strikingly, 46.6% of the 298 eosinophilia cases were probably neglected (and not even mentioned in the medical records) despite the fact that the level of eosinophils chosen for the selection of patients was high (≥ 1 G/L). A higher level of eosinophils was significantly more often taken into account. Thus, although the normal value of eosinophils is less than 0.4 or 0.6 G/L, this would suggest that most physicians do not pay attention to a transitory mild eosinophilia, unless it is associated with clinical or non-clinical disorders. The proportion of neglected cases would probably have been higher if we had retained a lower threshold value.

The most common cause observed was drug-related (24.5% of investigated eosinophilias), and the most frequently incriminated drug was allopurinol. Many other reactions (including DRESS) were related to antibiotics. These medications could have been over-represented as patients were selected (in part) from an infectious diseases unit. However, our results correspond to the international RegiSCAR study on DRESS [12] in which a high proportion of the 117 cases involved antibiotics and allopurinol. Noticeably, fever accompanied 90% of DRESS cases in the RegiSCAR study compared to only 60% in our own. This difference may be explained by the threshold value chosen to define fever (38°C for Kardaun et al. and 38.5°C for our study). In our study, drug-related eosinophilia was also associated with a significantly older age, which may be explained by the higher number of medications prescribed to older patients. However, as every age group was concerned, age should not be used as a determining factor in the diagnostic process.

A skin rash was reported in 78 patients, with strong implications on the diagnostic process but in different ways. First, in the presence of a skin rash, eosinophilia was more likely to be taken into account, which could be related to the fact that the leukocyte differential received

Table 4. Recommended examinations to explore eosinophilia according to seven previous studies. “Yes”: recommended first-line examination; “2nd”: recommended second-line examination.

Recommended exams	References						
	(1)	(7)	(8)	(9)	(11)	(13)	(14)
Control of blood count after one or two weeks		Yes		Yes		Yes	
Blood smear	2 nd			Yes		Yes	Yes
C-reactive protein		Yes		Yes		Yes	Yes
Serum creatinine		Yes		Yes			Yes
Liver function tests, bilirubin		Yes		Yes			Yes
Fibrinogen							Yes
Troponin	2 nd	Yes					2 nd
Electrocardiogram	2 nd						2 nd
Creatine phosphokinase				Yes			Yes
Serum tryptase	2 nd	2 nd					2 nd
Blood serum IgE	2 nd			Yes		Yes	
Immunoglobulin dosage						Yes	
Serum protein electrophoresis							2 nd
Anti-neutrophil cytoplasmic antibodies (ANCA)	2 nd	Yes				Yes	2 nd
Anti-nuclear antibodies (ANA)						Yes	2 nd
Rheumatoid factor						Yes	
B ₁₂ vitamin	2 nd						2 nd
Chest X-ray	2 nd	Yes			Yes	Yes	
HIV serology				Yes			Yes
HCV serology							Yes
HTLV-1 serology							2 nd
Stool sample (3 times)	Yes		Yes	Yes			
Stool sample (3 times in case of diarrhea or recent travel)		Yes			Yes	Yes	Yes
<i>Toxocara</i> serology		Yes		Yes			Yes
<i>Fasciola</i> serology				Yes			
<i>Trichinella</i> serology in the case of wild game consumption				Yes			Yes
<i>Schistosoma</i> , <i>Strongyloides</i> , and filariasis serology, in case of recent travel in tropical region			Yes	Yes	Yes		
“helminth serology oriented by recent travel destination”	Yes					Yes	Yes
<i>Strongyloides</i> serology	Yes		Yes				
Microfilaraemia in the case of recent travel to a tropical region			Yes	Yes			
<i>Schistosoma</i> eggs in urine sample (3 times) in the case of recent travel to a tropical region			Yes	Yes			

<https://doi.org/10.1371/journal.pone.0204468.t004>

more attention when a skin rash was present. Second, the combination of eosinophilia and skin rash was strongly associated with identifying an iatrogenic cause. This may be a key element in the diagnostic approach, as it could avoid excessive lab evaluation for patients who present eosinophilia with skin manifestations.

Helminth infections were not infrequent, but mostly concerned returning travelers. The only helminth identified in non-travelers was *Toxocara*, an ubiquitous zoonotic roundworm whose larvae can accidentally penetrate the human body. Only five stool examinations (in 76 patients) permitted the identification of a parasite (or its eggs), and all of them concerned travelers; this should be nuanced by the fact that many stool examinations were not performed the recommended three times. Our results suggest that helminth serologies are cost-effective labs in travelers (except for toxocariasis), as they allow the diagnosis of parasitosis to be strengthened or confirmed; *Schistosoma*, *Strongyloides*, and *Toxocara* serologies were particularly useful in comparison to others. Thus, we confirmed that helminth infections, though not rare,

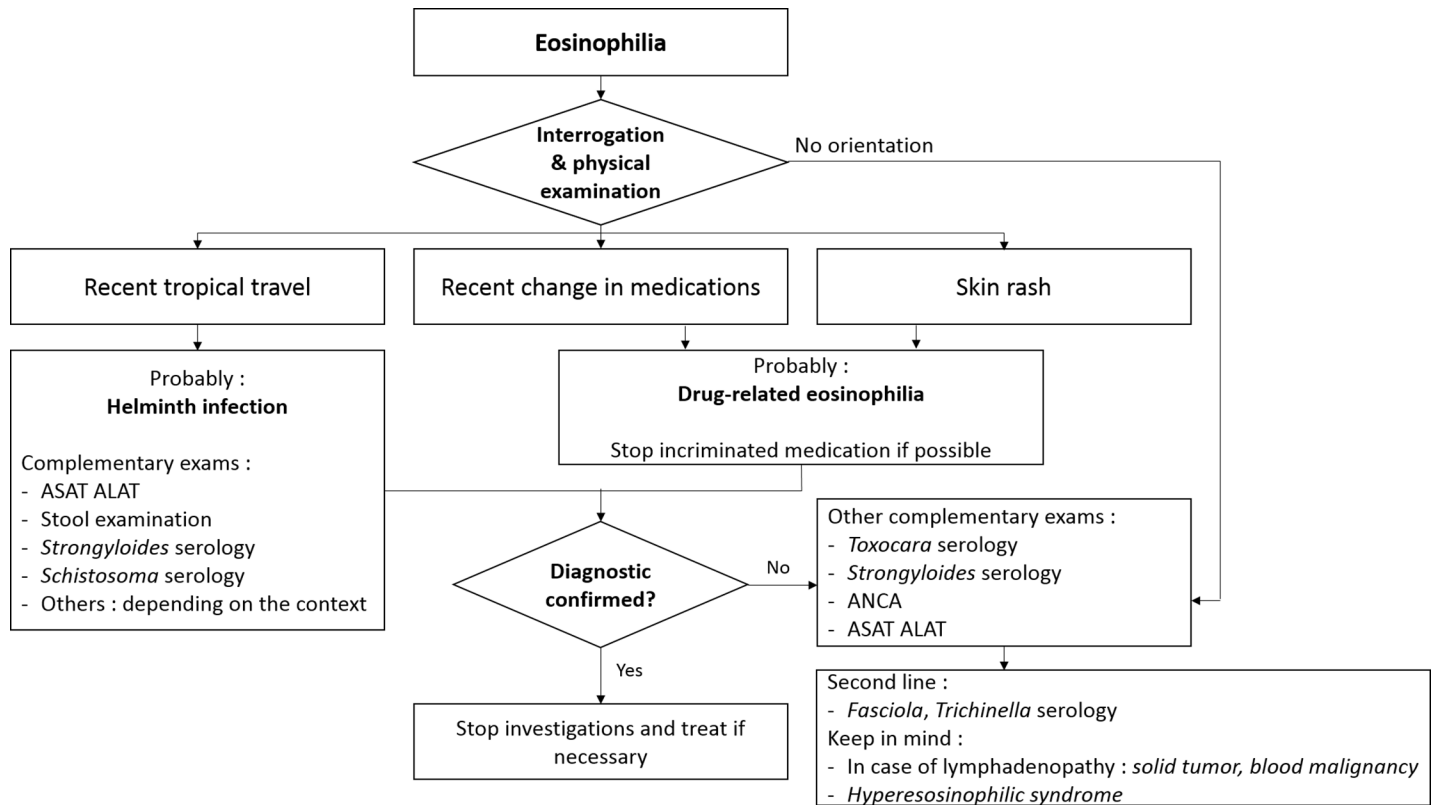


Fig 4. Proposed diagnostic approach.

<https://doi.org/10.1371/journal.pone.0204468.g004>

should be preferentially searched for in travelers. We propose for stool examinations and helminth serologies to be reserved for patients returning from a tropical country and/or with suggestive symptoms of a given helminth disease, excepting the *Toxocara* serology, which may be relevant in asymptomatic patients and non-travelers. The *Strongyloides* serology might also be performed early in the diagnostic process, because this disease can be discovered years after the travel during which the infection was acquired; the existence of a recent travel is then irrelevant. Despite the fact that hypereosinophilia is not associated with this disease, alveolar echinococcosis was investigated in many patients (probably because it is known to be endemic in our region). This parasite was never found among the 298 cases of eosinophilia in our study.

Vasculitis and other autoimmune diseases were not rare in this study, which may be due to the fact that patients were selected in part from an internal medicine department. However, this may also reflect the fact that these diagnoses are frequent in patients with eosinophilia >1 G/L; given the potentially severe complications of these diseases, anti-neutrophil cytoplasmic antibody testing should be performed early in these patients.

It is noteworthy that apart from allergy (including drug reaction), helminth infection, and vasculitis and other autoimmune diseases, more rare diagnoses should be kept in mind, including blood malignancy (particularly Hodgkin disease), and hypereosinophilic syndrome. Persistent eosinophilia in non-travelers patients not receiving any therapy should not be left aside, and such rarer diagnoses should always be evoked; the last is an exclusion diagnosis, and should be considered solely if other causes have been ruled out.

Even when eosinophilia was explored, many patients did not receive a diagnosis (25.7% of investigated cases), thus reflecting the difficulties encountered to identify the causes of

eosinophilia. The complexity of the diagnostic process is illustrated by the heterogeneity of different recommendations proposed in literature [1,7,8,9,11,13–14] (Table 4).

In previous studies, the frequencies of the diagnoses were different. In the study of Sade et al [15], on 100 patients with an eosinophilia above 0.650 G/l, drug reactions and helminth infections were less frequent (6% and 5%, respectively), whereas asthma and allergic diseases were more prevalent (13%); the proportion of unexplained eosinophilia and hypereosinophilic syndrome were higher than in our study (34% and 7%). In the study of Lombardi and Passalacqua [16], on 1862 patients with eosinophilia above 0.35 G/l, 79.7% of cases were related to asthma or allergy, 8.2% to helminth diseases, and 0.6% to autoimmune diseases. These major differences may be due to the low threshold of eosinophils chosen by the authors to select the patients, since asthma and allergy are more often correlated with mild eosinophilia. Strangely, no drug reaction were reported as cause of eosinophilia in this study.

Finally, we propose a strategy based on our results (Fig 4) that draws from skin changes, drug prescriptions, and recent travel history in tropical regions, as we observed that travel and drug reaction are prominent causes of eosinophilia. In case of lymph node enlargement, a diagnosis of neoplasm (prominently Hodgkin disease) should be considered in the first place.

Conclusion

Mild eosinophilia is often neglected. A diagnosis of drug-related reaction is frequently identified, particularly in case of rash. Apart from toxocariasis, helminth infections should be searched for (mostly by serology or stool examination) in travelers. ANCA should be performed early, as potentially severe vasculitis is not uncommon. Determination of serum IgE level is weakly informative.

Author Contributions

Conceptualization: Martin Peju, Hervé Pelloux, Olivier Epaulard.

Data curation: Martin Peju, Olivier Epaulard.

Formal analysis: Martin Peju, Olivier Epaulard.

Investigation: Martin Peju, Olivier Epaulard.

Methodology: Olivier Epaulard.

Supervision: Olivier Epaulard.

Validation: Hervé Pelloux, Olivier Epaulard.

Visualization: Olivier Epaulard.

Writing – original draft: Martin Peju, Olivier Epaulard.

Writing – review & editing: Alban Deroux, Hervé Pelloux, Laurence Bouillet, Olivier Epaulard.

References

1. Roufousse F, Weller PF (2010) Practical approach to the patient with hypereosinophilia. *J Allergy Clin Immunol* 126(1):39–44. <https://doi.org/10.1016/j.jaci.2010.04.011> PMID: 20538328
2. Brigden M, Graydon C (1997) Eosinophilia detected by automated blood cell counting in ambulatory North American outpatients. Incidence and clinical significance. *Arch Pathol Lab Med* 121(9):963–967. PMID: 9302929

3. Andersen CL, Siersma VD, Hasselbalch HC, Lindegaard H, Vestergaard H, Felding P, et al. (2013) Eosinophilia in routine blood samples and the subsequent risk of hematological malignancies and death. *Am J Hematol* 88(10):843–847. <https://doi.org/10.1002/ajh.23515> PMID: 23765950
4. Schulte C, Krebs B, Jelinek T, Nothdurft HD, von Sonnenburg F, Löscher T (2002) Diagnostic significance of blood eosinophilia in returning travelers. *Clin Infect Dis* 34(3):407–411. <https://doi.org/10.1086/338026> PMID: 11753824
5. Pardo J, Carranza C, Muro A, Angel-Moreno A, Martín A-M, Martín T, et al. (2006) Helminth-related eosinophilia in African immigrants, Gran Canaria. *Emerg Infect Dis* 12(10):1587–1589. <https://doi.org/10.3201/eid1210.060102> PMID: 17176579
6. Meltzer E, Percik R, Shatzkes J, Shatzkes J, Sidi Y, Schwartz E (2008) Eosinophilia among returning travelers: A practical approach. *Am J Trop Med Hyg* 78(5):702–709. PMID: 18458300
7. Chappuis S, Ribi C, Greub G, Spertini F (2013) [Peripheral blood eosinophilia: diagnostic value and further assessment]. *Rev Médicale Suisse* 9(382):819–825.
8. Checkley AM, Chiodini PL, Dockrell DH, Bates I, Thwaites GE, Booth HL, et al. (2010) Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. *J Infect* 60(1):1–20. <https://doi.org/10.1016/j.jinf.2009.11.003> PMID: 19931558
9. Savini H, Simon F (2012) [addressing hypereosinophilia]. *EMC Mal Infect* 9(4): 1–12.
10. Brigden ML (1999) A practical workup for eosinophilia. You can investigate the most likely causes right in your office. *Postgrad Med* 105(3):193–194, 199–202, 207–210. <https://doi.org/10.3810/pgm.1999.03.638> PMID: 10086043
11. Ridings H, Geisler WM (2006). Evaluating eosinophilia in the primary care setting. *JAAPA Off J Am Acad Physician Assist* 19(6):34–38.
12. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. (2013) Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 169(5):1071–1080. <https://doi.org/10.1111/bjd.12501> PMID: 23855313
13. Sims H, Erber WN (2011) Investigation of an incidental finding of eosinophilia. *BMJ* 342:d2670. <https://doi.org/10.1136/bmj.d2670> PMID: 21593088
14. Centre national de référence des syndromes hyperéosinophiliques (CEREO). [Diagnosis assesment of hypereosinophilia]. <http://www.reseau-eosinophile.fr/>. Accessed 16May 2018.
15. Sade K, Mysels A, Levo Y, Kivity S (2007) Eosinophilia: A study of 100 hospitalized patients. *Eur J Intern Med* 18(3):196–201. <https://doi.org/10.1016/j.ejim.2006.09.031> PMID: 17449391
16. Lombardi C, Passalacqua G (2003) Eosinophilia and diseases: clinical revision of 1862 cases.