Diagnostic Significance of Blood Eosinophilia in Returning Travelers

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This study was conducted to investigate the predictive value of blood eosinophilia (total white blood cell count with ⩾8% eosinophils) for the diagnosis of travel-related infections in 14,298 patients who returned from developing countries. The data show that blood eosinophilia in travelers returning from developing countries has only limited predictive value for the presence of travel-related infections. However, the likelihood of the presence of helminth infections increases considerably with the extent of eosinophilia.

Eosinophilia is defined as the presence of >500 eosinophils per μL of blood or as a WBC count in which >7% of the WBCs are eosinophilic leukocytes. It develops as an immunologically mediated response in association with diverse processes. Allergic disorders (such as atopic diseases and drug-related hypersensitive reactions), collagen vascular diseases, and malignancies are known to be associated with eosinophilia. As mentioned in medical literature, eosinophilia is seen especially in association with helminth infections, and during the tissue-invasive stages of development in particular [1].

Because of changing patterns of worldwide travel, an increasing number of physicians in industrialized countries are confronted with tropical-related diseases. Intestinal nematodes are among the most prevalent causes of infection in humans [2]. Infections tend to be chronic and to have high reinfection rates and are typically overdispersed, with patterns of intense infections being confined to minorities within the general population [3, 4]. In their study, Nokes et al. [5] showed that even children with moderately intense *Trichuris trichria* infection had improvements in their cognitive function (i.e., attentiveness, auditory short-term memory, long-term memory) after receiving treatment. Therefore, the availability of reliable and easy diagnostic tests for detection of helminthic infections could provide important tools for patient care.

The degree of eosinophilia in patients with helminthic infections may vary according to distribution, migration, maturation, and burden of the parasite. Various studies have showed different correlations between blood eosinophilia and multicellular pathogenic infections [6–8].

Patients and methods. In a retrospective analysis, we investigated the diagnoses and laboratory data for 14,298 patients. From January 1995 through December 1999, the patients had been transferred to the outpatient clinic of the Department of Infectious Diseases and Tropical Medicine of the University of Munich (Germany) after having returned mainly from developing countries (96.8% of patients).

All WBC differentials were performed microscopically. If more than 1 WBC differential was performed, the first eosinophil count was used for further analysis. Microscopic evaluation of samples of fresh stool, urine, blood smear, wounds, and skin defects was performed for detection of ova, parasites, and bacteria. Rectal mucosal snips and 24-h terminal urinalysis were performed for detection of *Schistosoma* ova, and skin snips were performed for detection of microfilariae of *O. volvulus.* Serological tests were performed for detection of fascioliasis, filariasis, hydatid disease, amebiasis, schistosomiasis, toxocariasis, and trichinosis. Antigen-capture ELISAs were performed to detect *Giardia lamblia* and *Entamoeba histolytica* antigen in stool samples. Not every patient underwent every investigation. In patients with eosinophilia, up to 3 stool samples were examined, and serological tests were performed to detect helminth disease.

Blood eosinophilia was defined using percentage of the total WBCs, because, for the detection of helminthic infections, the sensitivity and specificity were higher than were the sensitivity and specificity of the absolute eosinophilic cell count.

Results. Of 14,298 patients investigated, 689 (4.8%) had blood eosinophilia (i.e., eosinophils were ⩾8% of the total WBC count). The ratio of female patients to male patients was 1:1.77 (for the total patient population, the ratio was 1:1.05). The mean age at admission to the hospital was 34.3 years (range, 2–86 years). Of these travelers, 507 (73.6%) were born in Europe and 469 (68.1%) were German nationals.

The duration of travel varied from short (journeys of 3 days) to lengthy (stays of up to 32 years); the median duration of travel was 35 days. The investigation of travel destinations re-

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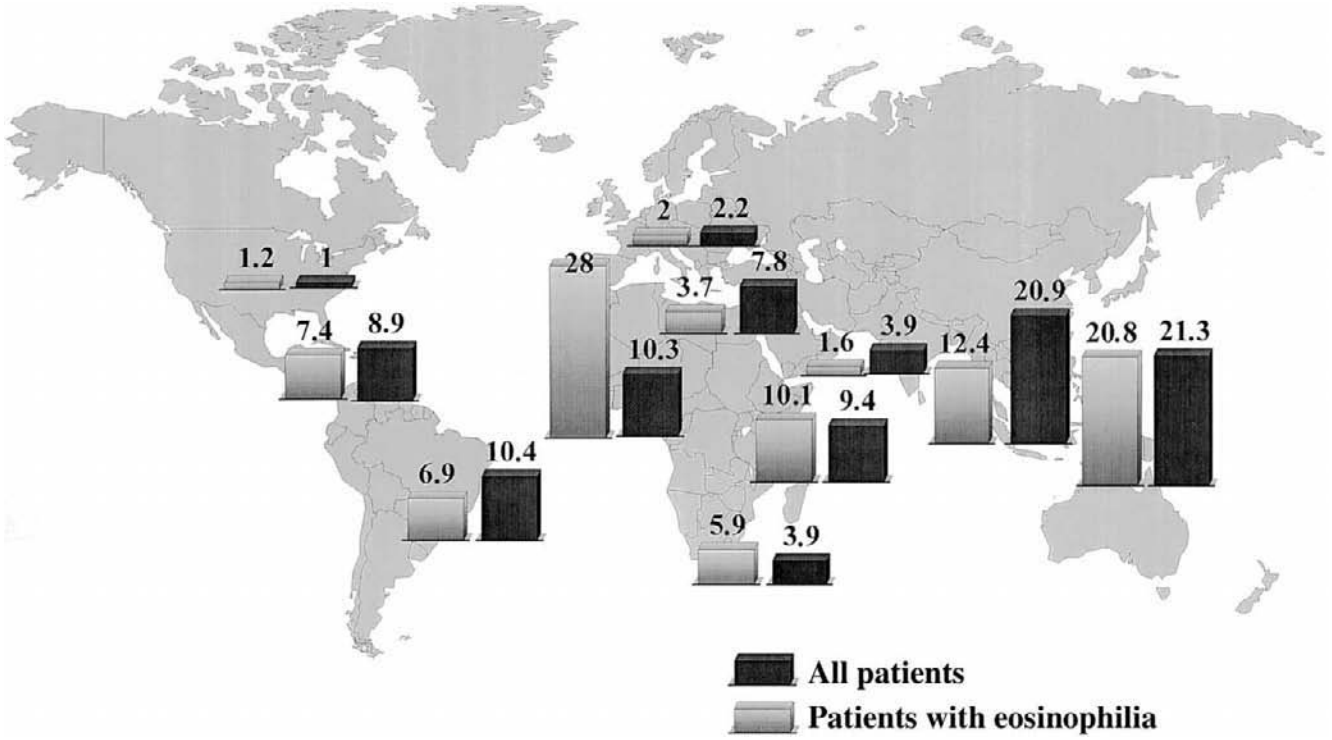

Figure 1. Travel destinations of patients with eosinophilia compared with those of the total patient population. Data are percentages of patients.

vealed that 329 patients (47.7%) with eosinophilia had traveled to Africa versus 4490 (31.4%) of all travelers screened. A total of 193 patients (28%) had previously been to West and central Africa, as compared with 1473 (10.3%) of all travelers (RR for travel to North Africa, 0.43 [95% CI, 0.29–0.64]; RR for travel to West Africa, 2.95 [95% CI, 2.52–3.46]; RR for travel to East Africa, 1.03 [95% CI, 0.81–1.31]; RR for travel to southern Africa, 1.45 [95% CI, 1.07–1.96]).

Of the 689 travelers, 240 (34.8%) returned from Asia (RR for travel to the Indian subcontinent, 0.39 [95% CI, 0.22–0.71]; RR for travel to Southeast Asia, 0.51 [95% CI, 0.41–0.64]; RR for travel to Indonesia, 0.91 [95% CI, 0.76–1.09]), and 107 (15.5%) returned from the Americas (RR for travel to North America, 1.1 [95% CI, 0.56–2.17]; RR for travel to Central America, 0.78 [95% CI, 0.59–1.04]; RR for travel to South America, 0.62 [95% CI, 0.47–0.83]; figure 1).

One-third (227 [33.0%]) of the patients with eosinophilia were asymptomatic at the time of presentation. The most common symptoms for the others were fatigue (in 168 patients [24.4%]), diarrhea (in 147 [21.3%]), and skin lesions (in 118 [17.1%]).

A definite diagnosis could be made for 248 patients (36.0%) with eosinophilia. The positive predictive value of the eosinophilia for helminth infection was 18.9%, and the negative predictive value was 98.7%. The probability of finding a definite diagnosis, however, reaches >60% when eosinophilic granulocytes constitute ⩾16% of the total WBC count (figure 2). When the proportion is greater than this level, the positive predictive value for helminth infections increases to 46.6%.

The mean percentage of eosinophils in the total WBC count was 11.0% (range, 8%–56%). We detected the highest eosinophil counts (mean, 17.8% of WBCs [1545 eosinophils per μL of blood]) in patients with helminth infections, and these in-

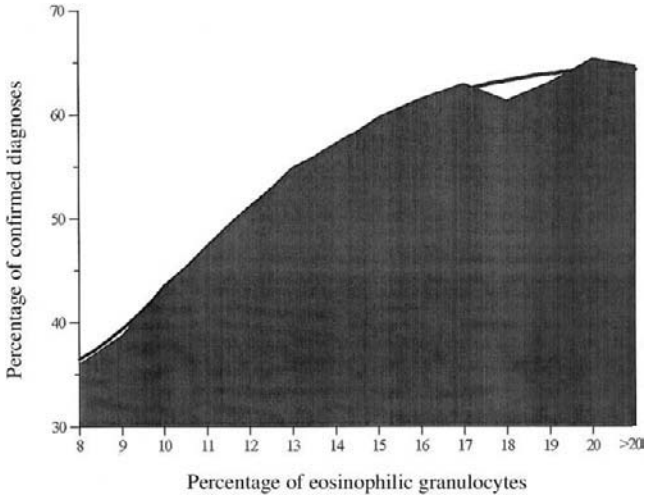

Figure 2. Probability of a definite diagnosis in relation to cumulative levels of eosinophils in the WBC count.

Table 1. Definite diagnoses for 689 patients with blood eosinophilia, from a total of 14,298 patients screened.

Disease	No. of patients	Mean eosinophil count		Region of travel				
		Percentage of WBCs	Eosinophils/ μL of blood	Africa	Asia	America	Europe	No data
Helminth infection	130	17.8	1545					
Hookworm	18	22.9	3063	9	2	5		2
Filariasis[a]	13	22.4	1448	7	1			5
Schistosomiasis	41	17.7	1497	34	3			4
Strongyloidiasis	15	16.1	1122	7	4	1		3
Ascariasis	7	12.9	1024	3	2	1		1
Cutaneous larva	17	12.5	924	2	9	5		1
Echinococcosis	2	12.5	717					2
Trichuriasis	4	11.5	874	1	1	2		
Enterobiasis	2	10.5	570					2
Other[b]	11	22.1	1789	3	3		2	3
Protozoal infection	56	12.1	846					
Amebiasis	26	13.5	985	12	7	2	1	4
Malaria	6	12.5	560	6				
Blastocystis	13	11.8	768	6	2	1		4
Giardiasis	11	9.9	764	4	5	1		2
Viral infection	10	13.3	547					
HIV	4	16.8	648	2				2
Hepatitis B	4	12.5	525	2				2
Dengue fever	1	8.0	272		1			
Other[c]	1	8.0	504	1				
Allergic disorders	22	11.2	783					
Urticaria	10	11.4	821	3	3	3		1
Asthma	5	11.4	622	3				2
Atopic eczema	5	11.2	839			1		4
Pollinosis	2	10.0	852	1	1			
Bacterial	27	10.5	851					
Pyodermas	13	11.9	990	4	2	3		4
Salmonellosis	1	10.0	640	1				
Campylobacter species	8	9.4	666	3	5			
Shigellosis	3	8.7	883	1	1			1
Urinary tract infection	2	8.5	751	1	1			
Ectoparasites (scabies)	2	9.5	744		2			
Immunological disorders (colitis ulcerosa)	1	8.0	1088					1

NOTE. Eosinophilia was defined as a WBC count with ⩾8% eosinophils. No diagnosis was made for 441 patients.

[a] Four cases of onchocerciasis, 1 case of loiasis, and 8 cases of other infections.

[b] Three cases of trichinellosis, 3 cases of taeniasis, 2 cases of fascioliasis, and 1 case each of toxocariasis, heterophyiasis, and hymenolepiasis.

[c] One case of herpes zoster.

fections also matched the greatest part (130 [52.4%] of 248) of all definite diagnoses (table 1); however, blood eosinophilia was present at the time of diagnosis in only 41.5% of the patients who had helminth infections diagnosed in the total patient population, and only 38.3% of all patients with helminth infections had blood eosinophilia with >500 eosinophils per μL of blood, although the number of patients with eosinophilia increased to 697 by use of the absolute eosinophilic cell count (vs. 689 patients, by use of the relative eosinophilic count; table 2).

Discussion. Overall, 31.4% of the total population returned from the African continent, as compared with 47.7%

Table 2. Frequency of eosinophilia in patients with travel-related infections and of other diagnoses among 14,298 patients screened.

Disease	No. of patients	No. (%) of patients with eosinophilia
Helminth infection	313	130 (41.5)
Strongyloidiasis	17	15 (88.2)
Filariasis[a]	20	13 (65.0)
Hookworm	29	18 (62.1)
Schistosomiasis	92	41 (44.6)
Cutaneous larva migrans	48	17 (35.4)
Ascariasis	29	7 (24.1)
Trichuriasis	27	4 (14.8)
Enterobiasis	14	2 (14.3)
Echinococcosis	22	2 (9.1)
Other[b]	15	11 (73.3)
Allergic disorder	72	22 (30.5)
Atopic eczema	9	5 (55.6)
Pollinosis	4	2 (50.0)
Urticaria	30	10 (33.3)
Asthma	29	5 (17.2)
Ectoparasites	8	2 (25.0)
Scabies	8	2 (25.0)
Viral infection	47	10 (21.2)
HIV	9	4 (44.4)
Hepatitis B	10	4 (40.0)
Dengue fever	24	1 (4.1)
Other[c]	4	1 (25.0)
Immunological disorder	10	1 (10.0)
Colitis ulcerosa	10	1 (10.0)
Bacterial infection	525	27 (5.1)
Pyodermas	80	13 (16.3)
Urinary tract infection	41	2 (4.9)
Campylobacter enteritis	173	8 (4.6)
Shigellosis	139	3 (2.2)
Salmonellosis	92	1 (1.1)
Protozoal infection	1140	56 (4.9)
Blastocystis hominis	149	13 (8.7)
Amebiasis	447	26 (5.8)
Malaria	160	6 (3.7)
Giardiasis	384	11 (2.9)

NOTE. Eosinophilia was defined as a WBC count with ⩾8% eosinophils.

[a] Five cases of onchocerciasis, 2 cases of loiasis, and 13 cases of other infections.

[b] Four cases of trichinellosis, 4 cases of taeniasis, 2 cases of fascioliasis, 2 cases of heterophyiasis, 2 cases of toxocariasis, and 1 case of hymenolepiasis.

[c] Four cases of herpes zoster.

of patients with eosinophilia; West and, especially, central Africa emerged as areas with increased risk. Visitors to the Indian subcontinent and Latin America are apparently at a markedly lower risk of developing eosinophilia (figure 1).

In only 36.0% of patients with eosinophilia could a definite diagnosis be made, and in only 18.9% could a specific helminth infection be detected. These results are comparable with those of Libman et al. [7], who found that 14% of their patients with eosinophilia had a demonstrable parasitic infection. On the other hand, Harries et al. [8] were able to find a helminth infection in 38.7% of white patients with blood eosinophilia returning from the tropics.

The explanation for the presence of blood eosinophilia in the patients we studied who did not have a diagnosed parasitic infection or other conditions commonly associated with eosinophilia remains speculative. A recent study from Brazil underlines the problem of diagnosing some helminth infections. The probability of finding *Strongyloides stercoralis* larvae was only 16% when 1 stool sample was examined, 24% when 2 samples were examined, and 47% when 4 samples were examined [9]. Allergic disorders could also be a likely explanation for modest eosinophilia in our patient population; however, specific tests (e.g., skin prick tests) for atopic conditions were not performed in this patient population.

Although helminth infections represent the greatest part of diagnoses (52.4%) in our patients with blood eosinophilia, and although they were also associated with the highest eosinophil levels (15.7% of total WBC count), in only 41.5% of all helminth infections in our total patient population was a blood eosinophilia present (tables 1 and 2). This shows that helminth infections often occur without blood eosinophilia. One reason may be the fact that several parasites induce high-grade blood eosinophilia only during the tissue-invasive stages of their development [10–15]. In a recent study from the United Kingdom, blood eosinophilia was present at the time of diagnosis in only 44% of 1107 travelers and immigrants with schistosomiasis [16]. These results match our observations exactly.

The results of our study show that, in a patient with high-grade blood eosinophilia returning from the tropics, there is significant likelihood of a travel-related infection, and of a helminth infection in particular. The diagnostic value of blood eosinophilia is limited, however, because a definite diagnosis could be made for only 36.0% of patients with eosinophilia, and not even one-half of all patients with helminth infections had blood eosinophilia at the time of diagnosis.

We conclude that the diagnostic significance of blood eosinophilia in patients returning from developing countries is limited. For a case of eosinophilia in which eosinophils constitute ⩾16% of the WBC count, however, the probability for a travel-related diagnosis increases to >60% and the positive predictive value for helminth infection increases to 46.6%. Nevertheless, blood eosinophilia in these patients is only 1 of many diagnostic hints, and the extent and direction of the diagnostic work-up have to be guided independently by additional data on risk and exposure, clinical signs and symptoms, and other laboratory results.

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