UNIVERSITÉ DE LILLE

FACULTÉ DE MÉDECINE HENRI WAREMBOURG

Année : 2021

THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Manifestations cliniques des éosinophilies parasitaires

Présentée et soutenue publiquement le 24 novembre à 18 heures
au Pôle Recherche

par Charles MIDOL

JURY

Président :

Monsieur le Professeur Éric HACHULLA, PU-PH

Assesseurs :

Monsieur le Professeur Boualem SENDID, PU-PH

Madame le Docteur Fanny VUOTTO, PH

Directeur de thèse :

Monsieur le Docteur Guillaume LEFEVRE, MCU-PH

AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses :

celles-ci sont propres à leurs auteurs.

SOMMAIRE

ABRÉVIATIONS FRANÇAISES

CHU	Centre Hospitalier Universitaire
COHESion	Cohorte nationale des syndromes hyperéosinophiliques
GEPA	Granulomatose éosinophilique avec polyangéite
EO	Éosinophilie
HE	Hyperéosinophilie
IL	Interleukine
SHE	Syndrome hyperéosinophilique

ABRÉVIATIONS ANGLAISES

ABPA	Allergic Bronchopulmonary Aspergillosis
AEC	Absolute eosinophil count
AERD	Aspirin Exacerbated Respiratory Disease (Widal or Samter's triad)
CK	Creatinine kinase
COHESion	national COhort of hypereosinophilic syndrome patients
CRP	C reactive protein
EGPA	Eosinophilic Granulomatosis with Polyangiitis
ELISA	Enzyme-Linked Immunosorbent Assay
EO	Eosinophilia
Eo-R	Eosinophil-related
HE	Hypereosinophilia
HES	Hypereosinophilic syndrome
HRCT	High-Resolution Computerized Tomography
ICOG-EO	International Cooperative Working Group on Eosinophil Disorders
IEP	Immunoelectrophoresis
iHES	Idiopathic Hypereosinophilic syndrome
IL	Interleukin
IQR	Interquartile range
MRI	Magnetic resonance imaging
Pa-R	Parasite-related
SD	Standard deviation
TNF	Tumour necrosis factor
WB	Western blot

INTRODUCTION

1. Parasitoses et éosinophilies secondaires : généralités

L'éosinophilie (EO), définie comme un taux d'éosinophiles circulants supérieur à 500 cellules/mm^3 ou 0,5 x 10^9/L (1,2) est un motif habituel de recours à la médecine interne. Les causes d'EO sont multiples et se révèlent le plus souvent réactionnelles c'est-à-dire secondaires à une maladie sous-jacente : atopie ou terrain allergique, réactions d'hypersensibilité (médicamenteuses ou non), collagénoses et vascularites, aspergillose broncho-allergique ou néoplasies sont les causes classiquement citées (3). Plus fréquemment dans les pays tropicaux (4) qu'en Europe ou en Amérique du Nord, l'éosinophilie est secondaire à une infection parasitaire (5). Parmi celles-ci, les helminthes (terme vernaculaire regroupant plusieurs taxons ayant pour point commun une forme de vers) partagent la particularité d'induire un mécanisme de régulation immunitaire par le biais des lymphocytes T régulateurs et une réponse Th-2 (6) conduisant à la production des cytokines associées (IL-4, IL-5, IL-9 et IL-13) et au recrutement d'éosinophiles. La classification actuelle des maladies à éosinophiles utilisée pour le soin et la recherche est celle proposée en 2011 par le Groupe de travail coopératif international sur les maladies à éosinophiles (ICOG-Eo). Cette classification distingue une EO (>500/mm3 d'une hyperéosinophilie (HE, >1 500/mm^3) et d'un syndrome hyperéosinophilique (SHE). Un SHE est donc défini par une HE sanguine ≥ 1 500/mm^3, d'évolution prolongée (≥ 1 mois) associée à des dommages tissulaires en rapport avec la toxicité des éosinophiles. Il s'agit d'une entité hétérogène qui comprend notamment les SHE néoplasiques « clonaux » (dont la leucémie chronique à éosinophiles liée à la délétion 4q12 responsable de la fusion FIP1L1-PDGFRA (F/P)) et les SHE « réactionnels » ou « secondaires » causés par une infection parasitaire, une prise médicamenteuse, une maladie inflammatoire ou néoplasique. Ce travail s'intéressera aux EO d'origine parasitaire dont nous allons décrire le spectre des manifestations cliniques.

2. Les parasitoses responsables d'éosinophilies secondaires

Les helminthes responsables d'Eo secondaires sont listés dans le **Tableau 1**. Les plus fréquemment rencontrés en dehors des zones d'endémies sont la toxocarose, la distomatose, la trichinose et l'anisakidose pour les parasitoses autochtones, et la bilharziose, l'anguillulose et la filariose qui sont des cas d'importation car absentes dans notre région.

Tableau 1. Helminthiases les plus fréquentes, prévalence globale et zone d'endémie parasitaire. D'après Hotez J. et coll.(7)

Disease	Major etiologic agent	Global prevalence	Regions of highest prevalence
Soil-transmitted nematodes			
Ascariasis	*Ascariasis lumbricoides* (roundworm)	807 million	Developing regions of Asia, Africa, and Latin America
Trichuriasis	*Trichuris trichiura* (whipworm)	604 million	Developing regions of Asia, Africa, and Latin America
Hookworm	*Necator americanus*; *Ancylostoma duodenale*	576 million	Developing regions of Asia, Africa, and Latin America (especially areas of rural poverty)
Strongyloidiasis	*Strongyloides stercoralis* (thread worm)	30–100 million	Developing regions of Asia, Africa, and Latin America (especially areas of rural poverty)
Filarial nematodes			
LF	*Wuchereria bancrofti*, *Brugia malayi*	120 million	Developing regions of India, Southeast Asia, and sub-Saharan Africa
Onchocerciasis (river blindness)	*Onchocerca volvulus*	37 million	Sub-Saharan Africa
Loiasis	*Loa loa*	13 million	Sub-Saharan Africa
Dracunculiasis (guinea worm)	*Dracunculus medinensis*	0.01 million	Sub-Saharan Africa
Platyhelminth flukes			
Schistosomiasis	*Schistosoma haematobium*, *Schistosoma mansoni*; *Schistosoma japonicum* (blood flukes)	207 million	Sub-Saharan Africa Sub-Saharan Africa and Eastern Brazil China and Southeast Asia
Food-borne trematodiases	*Clonorchis sinensis* (liver fluke); *Opisthorchis viverinni* (liver fluke); *Paragonimus spp.* (lung flukes); *Fasciolopsis buski* (intestinal fluke); *Fasciola hepatica* (intestinal fluke)	>40 million	Developing regions of East Asia
Platyhelminth tapeworms			
Cysticercosis	*Taenia solium* (pork tapeworm)	0.4 million (Latin America only)	Developing regions of Asia, Latin America, and sub-Saharan Africa

LF: lymphatic filariasis.

2.1. **L'ascaridiose** (infection à *Ascaris lumbricoides* ou *A. suum*) est l'helminthiase la plus répandue et touche entre 800 millions et un milliard de personnes (8) à l'échelle de la planète. Ce parasite transmis par l'alimentation dans des conditions d'hygiène insuffisante est responsable d'une morbi-mortalité importante notamment en raison de ses complications digestives (occlusions intestinales, saignements et perforations digestives, pancréatites aiguës).

2.2. **La toxocarose**, décrite pour la première fois par Wilder en 1950 (9) est l'infection par des larves de *Toxocara canis* ou *T. cati* respectivement transmises par les déjections de chiens et de chats. Elle est largement répandue et constitue l'helminthiase la plus fréquente dans les pays développés. Ses manifestations cliniquement sont extrêmement variées et secondaires à la migration parasitaire par voie sanguine (10), s'accompagnant typiquement d'une EO importante (11). Il d'usage de différencier le *larva migrans* viscéral se manifestant par des symptômes digestifs, respiratoires ou cutanés du *larva migrans* oculaire (migration oculaire, souvent unilatérale associée à une réaction inflammatoire pouvant conduire à la cécité) et la toxocarose *commune*, aspécifique correspondant à un tableau d'altération de l'état général associé à des symptômes digestifs, respiratoires ou cutanés parfois discrets (12).

2.3. **La bilharziose** (ou schistosomiase) doit son nom au pathologiste allemand Theodor Bilharz qui l'a découverte en 1851. Les parasites du genres *Schistosomia* sont transmis lors des baignades en eau douce dans les zones d'endémie (Afrique, Proche-Orient, Amérique du Sud et Asie) et sont présents chez environ 230 millions de personnes dans le monde (13,14). *Schistosomia mansoni* et *S. japonicum* sont responsables de formes digestives, d'évolution aiguë ou chronique tandis que *S. haematobium* est responsable des formes urogénitales se manifestant par des hématuries macroscopiques récidivantes dues à une réaction granulomateuse vésicale pouvant évoluer vers une néoplasie.

2.4. Le terme **Filariose** regroupe plusieurs infections à nématodes filariens, transmis par les piqûres d'insectes, et responsables des manifestations cutanées, lymphatiques et oculaires. Les filaires lymphatiques (*Wuchereria bancrofti*, *Brugia*

malayi et *timori*) sont responsables d'un lymphœdème chronique pouvant évoluer vers l'éléphantiasis et sont une cause importante de handicap dans les zones d'endémie parasitaire (15). La loase, due au parasite *Loa loa*, est présente uniquement en Afrique centrale et occidentale, se manifestant par des œdèmes migratoires et fugaces (dits de Calabar) ou par des réactions liées à la migration oculaire (16). L'onchocercose ou « cécité des rivières » est provoquée par *Onchocerca volvulus* présent en Afrique subsaharienne mais également en Amérique, responsable d'un prurit féroce conduisant typiquement à un aspect de pachydermie et de dyschromie. Sa gravité est liée à l'atteinte oculaire (17,18).

2.5. La **distomatose** ou fasciolose est une infection par la grande douve du foie (*Fasciola hepatica*), endémique en Europe, dont l'homme est un hôte accidentel, contaminé lors de la consommation de végétaux crus (cresson, mâche, pissenlits). La douve présente une affinité particulière pour le tube digestif et les canaux biliaires qu'elle peut infecter de façon aigue ou chronique, responsable de symptômes digestifs plus ou moins bruyants. Le traitement est médical et parfois chirurgical (19).

2.6. **L'anguillulose** ou strongyloïdose, est due au parasite *Strongyloides stercolaris*, présent dans les régions tropicales et subtropicales. La contamination est transcutanée et résulte d'un contact avec un sol souillé par les larves du parasite. Lorsqu'elle est symptomatique, l'infection se traduit par des signes digestifs, respiratoires et cutanés (8). Dans des rares cas, surtout chez l'immunodéprimé, l'évolution est dramatique, on parle alors d'anguillulose maligne.

2.7. **La trichinose** ou trichinellose est une infection à *Trichinella spiralis* transmis par l'ingestion de viande de porc ou de gibier insuffisamment cuite ou simplement fumée. La parasitose est endémique en Europe et en Amérique du Nord mais son incidence est en forte diminution (20). Elle se manifeste par des petites épidémies suite à un repas commun, où après une incubation de 24 à 48h, se développent des symptômes digestifs ainsi qu'une urticaire et un œdème de la face (21). Le tropisme musculaire du parasite explique l'apparition, typiquement deux semaines après le contact, de myalgies avec de rares atteintes cardiaques.

2.8. **L'anisakidose** est secondaire à l'ingestion d'*Anisakis simplex*, parasite du poisson. L'infection est présente chez les consommateurs de poisson cru en Europe du Nord et au Japon, elle se manifeste soit par une infestation gastrique dont les premiers symptômes surviennent quelques heures après l'ingestion, soit par une atteinte digestive responsable de tableaux pouvant mimer une appendicite ou une iléite et évoluer vers la péritonite (22). Les larves d'*Anisakis* sont également responsables de manifestations allergiques pouvant aller jusqu'au choc anaphylactique (23).

3. Difficultés diagnostiques des parasitoses responsables d'éosinophilies secondaires

La multiplicité des atteintes d'organes peut rendre le diagnostic étiologique difficile. Le tableau clinique est parfois limité à une atteinte d'organe : cutanée seule (urticaire, angioedème...), myocardite à éosinophiles, pneumopathie à éosinophiles, et peut faire évoquer en raison d'une hyperéosinophilie sanguine majeure un SHE idiopathique ou une granulomatose éosinophilique avec polyangéite (GEPA). La complexité du diagnostic parasitologique ne simplifie pas l'élimination des diagnostics différentiels. Il faut prendre

en compte un faisceau d'arguments épidémiologiques (séjour en zone d'endémie, consommation d'aliments à risque, pratique de la baignade en eau douce…), cliniques (l'œdème périorbitaire et les myalgies sont évocateurs d'une trichinose, les œdèmes de Calabar d'une loase) et biologiques.

Ce diagnostic biologique reste le plus délicat. Les tests sérologiques sont sensibles mais parfois peu spécifiques (réaction croisées), des tests de confirmation ne sont pas toujours disponibles ou standardisés, la mise en évidence directe du parasite est inconstante. Les examens directs des selles peuvent également être pris en défaut, car l'éosinophilie survient au moment de la migration tissulaire des larves : les œufs ou les vers adultes sont alors souvent indétectables dans les selles au moment de l'éosinophilie, comme illustré par la courbe de Lavier. D'autres parasites comme *Toxocara canis* ne sont pas détectables dans les selles, l'homme étant une impasse parasitaire avec un blocage au stade larvaire.

4. **Objectifs**

Il n'existe que peu de données sur les conséquences de l'éosinophilie sanguine et tissulaire au cours des helminthiases. En effet, la description des complications d'organes est limitée à de petites séries, ciblées soit sur une parasitose, soit sur un contexte clinique particulier (zone d'endémie parasitaire, populations migrantes...). L'objectif de ce travail de thèse était donc de décrire le spectre des atteintes d'organes induites par l'éosinophilie tissulaire au cours des helminthiases rencontrées chez des patients consultant dans un hôpital universitaire de France métropolitaine.

ABSTRACT

The clinical spectrum of eosinophil-related manifestations in helminthiases: a single center case series of 131 patients in North of France

Objectives: Helminthiases are a common cause of eosinophilia with a wide spectrum of clinical manifestations. The aim of our study was to describe the symptoms associated with helminthiasis in patients consulting a university hospital in metropolitan France, and to analyse them according to the parasite involved and the blood eosinophil count.

Methods: In this monocentric retrospective study, patients were included in case of diagnosed helminthiasis, with an eosinophilia (EO) > 0.5 x 10^9/L on at least one occasion. Patients were identified through the database of the parasitology laboratory of the University Hospital of Lille over the period 2010 to 2020. In the absence of any other explanation for the eosinophilia, the diagnosis of helminthiasis was retained in case of a positive serological test, and with (i) a confirmation test, and/or (ii) in case of evocative clinical criteria, and (iii) when the follow-up of the patient concluded to the efficacy of the antiparasitic treatment, which had to exclude the alternative diagnoses. For each patient, clinical, demographic and biological data, history of allergic manifestations, contact with pets and use of antiparasitic drugs and/or corticosteroid treatment were collected retrospectively. To discuss the distribution of clinical manifestations, a comparison group of patients with idiopathic HES was formed from the national CEREO cohort.

Results: One hundred and thirty-one patients (34% female) were included, with a median age [2;91] of 51 years. Of these patients, 31 (24%) had an allergic disorder (asthma, atopic disease or allergic reaction). Toxocariasis was the most common disease (n=73), followed by schistosomiasis (n=25), filariasis (n=10), fascioliasis (n=9), strongyloidiasis (n=8), trichinosis (n=5) and one case of anisakiasis. During the course of toxocariasis, the manifestations were cutaneous (34% of cases), respiratory (18%), gastrointestinal (15%), vascular (7%) with essentially thromboembolic manifestations (7% venous thrombosis, 1 case of arterial thrombosis) and cardiac (1%). Of all the parasitic infections, 27 (21%) patients had completely asymptomatic hypereosinophilia, and only 8 patients received systemic corticosteroids. Comparison of symptomatic helminthiasis and hypereosinophilia (N=52) with the CEREO idiopathic SHE cohort (N=148) showed similar frequencies of cutaneous, gastrointestinal, respiratory and vascular involvements, excepted cardiac involvement which was less frequent in parasitic infections (4% vs 30%, p<0.001). The eosinophil count was significantly higher in symptomatic patients compared with asymptomatic ones (median 1.7 [IQR 1.0-4.0] versus 1.2 [IQR 1.1-1.7] x 10^9/L; p=0.037).

Conclusion: Beyond the features suggestive of certain parasitosis, the clinical manifestations related to eosinophilia are comparable to those of idiopathic HES, and more frequent with higher blood eosinophil counts, underlining the central role of eosinophils in the occurrence of organ involvement.

INTRODUCTION

Blood eosinophilia is a common condition in clinical practice and could lead to various clinical features. A significant proportion of reactive eosinophilia is related to parasitic infections, especially in tropical countries (4,24,25) but also in western countries in immigrants (26) or international travellers (27).

Among parasitic diseases, helminths infections are characterized by the activation of Th-2 type cells leading to cytokines secretion (including Interleukin(IL)-4, IL-5 and IL-13). IL-5 contributes particularly to peripheral (blood) and tissue eosinophilia (6). Eosinophil related toxicity is well-known especially concerning vascular endothelium (28). However, studies in eosinophil-ablated mouses show conflicting roles of eosinophil in protective immunity and pathogenesis and the relative roles of parasites and eosinophils in organ damages is partially unknown (29).

From a clinical point of view, it is sometimes difficult to distinguish between eosinophil-related and parasite-related manifestations. Furthermore, few data exist on the consequences of blood and tissue eosinophilia in the context of helminthiasis. Indeed, the description of organ complications is limited to small series, either targeted on a parasitosis, or targeted on a particular clinical context (parasitic endemic area, migrant populations...).

The objectives of our study were: (i) to describe the eosinophil-related clinical manifestations of the most common helminthiasis in patients consulting in a French metropolitan university hospital, (ii), to compare the eosinophil-related clinical manifestations of helminthiasis with that of idiopathic hypereosinophilic syndromes.

Patients and eligibility criteria

Patients were identified thanks to a screening in the electronic database of the Department of Parasitology of the Lille University Hospital between January 2010 and December 2020, using the following serological tests:

- Toxocariasis: *Toxocara canis* IgG-ELISA, ELISA/NovaTec; NovaTec Immundiagnostica, Dietzenbach, Germany;
- Schistosomiasis: *Schistosoma mansoni* IgG-ELISA, ELISA/NovaTec; NovaTec Immundiagnostica, Dietzenbach, Germany; and/or indirect hemagglutination test using erythrocytes coated with *S. mansoni* adult worm antigens (Fumouze Diagnostics, Levallois-Perret, France);
- Filariasis: *Acanthocheilonema viteae* IgG-ELISA, Bordier Affinity Products, Crissier, Switzerland; or indirect hemagglutination (Fumouze Diagnostics, Levallois-Perret, France);
- Fasciolosis: *Fasciola hepatica* IgG-ELISA, Fumouze Diagnostics, Levallois-Perret, France;
- Strongyloidiasis: *Strongyloides spp.* IgG-ELISA, Scimedx Corporation, Dover (NJ), USA;
- Trichinosis: *Trichinella spiralis* IgG-ELISA, ELISA/NovaTec; NovaTec Immundiagnostica, Dietzenbach, Germany.
- Anasikiasis: *Anisakis spp* immunoelectrophoresis.

After screening of the medical charts, patients were excluded when they did not have eosinophilia (AEC < 0.5 $x10^9$/L), in case of loss of follow-up and/or with missing clinical data, and in case of an alternative diagnosis for eosinophilia: blood cancer

(including leukemia, lymphoma, myeloma, myelodysplastic or myeloproliferative syndromes), bullous pemphigoid, eosinophilic granulomatosis with polyangiitis (EGPA), IgG4-related disease, ABPA, eosinophilic fasciitis, and immune-related induced EO in patients treated for neoplasia.

Diagnosis of parasitic diseases

The parasitosis diagnosis was considered as definite (i) in case of microscopic demonstration of viable eggs in stool samples or filtered urine *(Schistosoma spp*.), microfilariae in a blood smear, mature worms in stool samples (*Ascaris spp*), OR (ii) in case of positive serological assay (screening test) and (iii) in presence of additional diagnosis criteria (a positive confirmation test or a highly suggestive clinical feature) (**Table 2**). For Toxocariasis, a positive western-blot assay (WB, LDBIO Diagnostics, Lyon, France) with at least 3 antigenic bands was required for definite diagnosis (30). For Schistosomiasis, a positive Immunoelectrophoresis (IEP, LDBIO Diagnostics, Lyon, France) or WB (LDBIO Diagnostics, Lyon, France) was required. For filariasis, the diagnosis was confirmed if the patient reported a stay in a parasite endemic area and/or a positive IEP and/or the presence of Calabar swelling and/or the presence of ocular symptoms; for Strongyloidiasis: a stay in an endemic area; for Trichinosis: the evidence of facial oedema, myalgias, or elevated creatine kinase; for Anisakiasis: the finding of gastrointestinal symptoms.

Table 2. Diagnostic criteria of helminthiasis in the study

Helminthiasis	Serological test	Confirmation test (if available)	Additional criteria
Toxocariasis	IgG-ELISA anti-*Toxocara canis*	**AND** Western blot *Toxocara* with 3 to 5 antigenic bands	-
Schistosomiasis	IgG-ELISA anti *Schistosoma mansoni* or indirect hemagglutination	**AND** Immunoelectrophoresis *Schistosoma* or western blot	**AND/OR** direct proof of *Schistosoma mansoni* or *haematobium* in stool or urine sample
Filariasis	IgG-ELISA anti *Acanthocheilonema viteae* or indirect hemagglutination	**AND/OR** immunoelectrophoresis	**AND** stay in endemic area **AND/OR** Calabar oedema **AND/OR** ocular symptoms
Fasciolosis	IgG-ELISA anti *Fasciola hepatica*	-	-
Strongyloidiasis	IgG-ELISA *Strongyloides spp*.	-	**AND** stay in endemic area
Trichinosis	IgG-ELISA anti *Trichinella spiralis*	**AND/OR** Western blot *Trichinella*	**AND** face oedema or myalgia with CK elevation
Anisakiasis	-	Immunoelectrophoresis *Anisakis spp*.	**AND** gastrointestinal symptoms

Patients who did not fulfil these criteria, and/or for who a final diagnosis of parasitic infection was not confirmed at the end of follow-up i.e. without normalisation or significant decrease of the AEC between 6 and 12 months (< 1.0 x 10^9/L and at least 50% decrease in case of HE, < 0.5 x 10^9/L otherwise) and/or with persistent symptoms after antiparasitic treatment were considered as having an uncertain diagnosis and were not included.

The following data were retrospectively collected in medical charts: age, sex, stay in parasitic endemic area, allergic disorders (defined as asthma, atopic dermatitis, rhinitis or drug and food allergies), exposure to dogs, cats and other pets, biological data (CRP level, maximal AEC and at 6-12 months after antiparasitic treatment), and treatment by anti-helminthic drugs and/or corticosteroids.

Eosinophil-related organs involvement assessment

For each patient, the eosinophil-related (Eo-R) organ damages were considered in case of symptoms, biological, radiological and pathological findings suggestive of reactive HES symptoms, i.e. unspecific to a given parasitic infection and similar to idiopathic HES symptoms. The considered Eo-R were dermatological like pruritus, rash (macular, papular or maculo-papular, urticaria, erythroderma), angioedema (facial or limb recurrent swellings); gastrointestinal symptoms (even if endoluminal parasites could explain some of them) including diarrhoea, abdominal pain, icterus, ascites; cardiac and vascular complications like venous or arterial thrombosis, endomyocardial fibrosis, myocarditis or pericarditis. Conversely, specific parasite-related (Pa-R) manifestations, including macroscopic haematuria in infection by *Schistosomia haematobium*, cutaneous or conjunctival *larva migrans*, uveitis, liver abscesses and parasitic brain pseudo-tumour. Muscular involvement including myalgias, elevated creatin kinase or necrotizing myositis (MRI and electro-myographic proven) and constitutional symptoms (fever, weight loss of > 5%) were separately classified. A patient was considered asymptomatic when he did not develop any Eo-R, Pa-R, muscular or constitutional symptoms.

Control cohort with idiopathic HES patients

We used the data from the French cohort COHESion (national cohort of hypereosinophilic syndrome patients, NCT04018118). At the time of finalizing the present study (August 2021), this cohort consisted of 148 patients of both sexes and of any age meeting the IHES diagnostic criteria according to the International Cooperative Working Group on Eosinophil Disorders (ICOG-EO) consensus conference (31). The clinical or biological manifestations associated with idiopathic HES were known for the patients included in this registry, notably cutaneous, gastrointestinal, respiratory, vascular and cardiac.

Statistical analysis

Categorical variables are expressed as numbers (percentages) and quantitative variables are expressed as median (interquartile range). Normality distribution was assessed graphically and using the Shapiro-Wilk test. Comparisons of parameters between several groups were done using the Kruskal–Wallis test followed by post hoc Dunn's tests for quantitative measures and chi-squared test (or Fisher's exact test in cases of expected cell frequency <5) for responder rates. Statistical tests were done at the two-tailed α level of 0.05. No correction for multiple testing was carried out. Data analyses and graphs were performed using the GraphPad Prism software version 9.1.2 (GraphPad Software, La Jolla, CA, USA).

Ethical considerations

Our study complies with Institutional ethical standards and those of the national research committee. For this type of study, authorisation from an Institutional Review Board was not required and all collected data were anonymized in compliance with French Regulation. Data collection and archiving were realized in accordance with the *Commission National de l'Informatique et des Libertés* (CNIL) guidelines.

General characteristics

Four hundred and twenty-nine positive results of serology were identified thanks to a screening in the electronic database. After exclusion of duplicates, patients lost of follow up and/or with missing data, patients with AEC < 0.5 x 10^9/L (**Supplementary Table 4**), and patients with a potential alternative diagnosis for eosinophilia (**Supplementary Table 5**), a total of 131 patients with 7 different helminthiases were included (**Figure 1**): Toxocariasis (N=73), Schistosomiasis (N=25), Filariasis (N=10), Fasciolasis (N=9), Strongyloidiasis (N=8), Trichinosis (N=5), Anisakiasis (N=1). The median age at diagnosis was 56 [2-91] years with 16 patients under the age of 18 years (12%) and a predominance of males (n=87, 66%). For 27 patients (20%), a contact with a domestic animal was documented, 69 (53%) had stayed in endemic area, a history of allergic disorder was reported for 31 patients (24%).

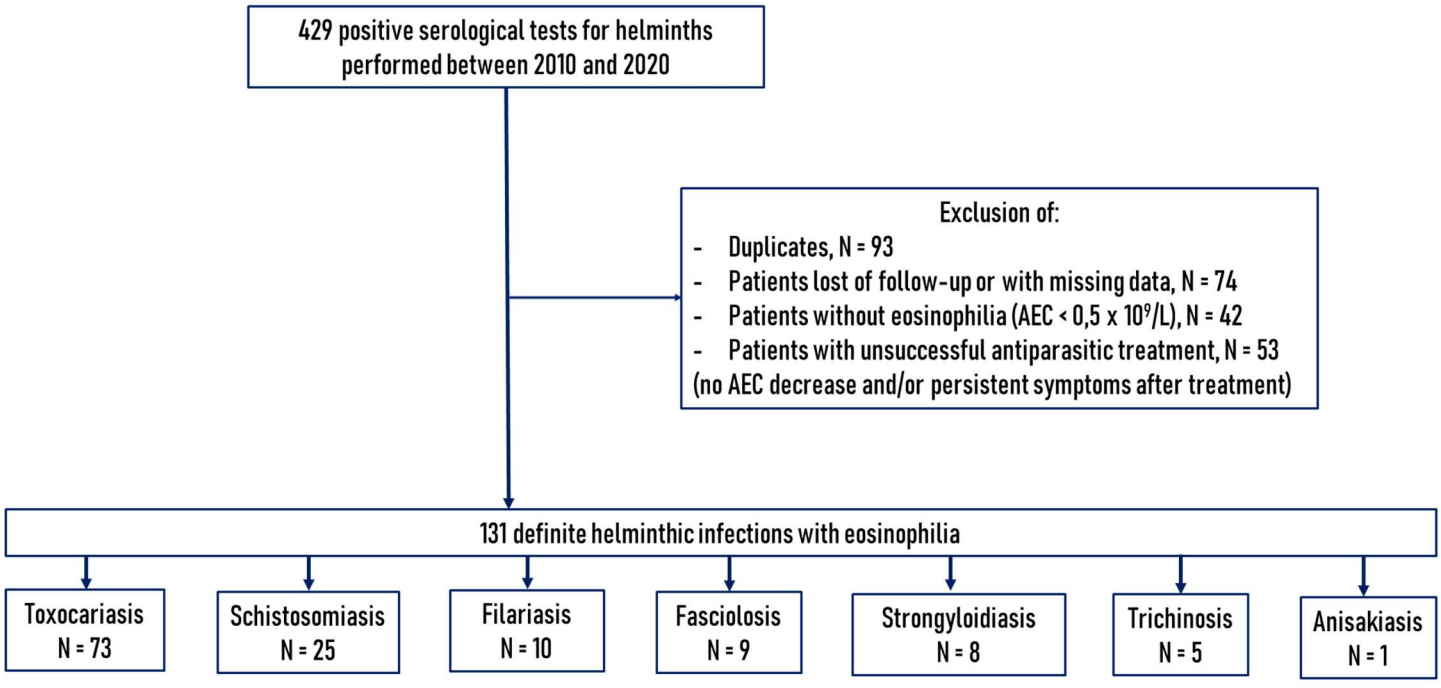

Figure 1. Study flow-chart.
AEC: Eosinophils absolute count.

The demographic, clinical and biological characteristics of each population are detailed in **Table 3**. Among the 88 patients who were diagnosed with an infection presumed to have been contracted in metropolitan France (toxocariasis, fasciolosis, trichinosis and anisakiasis), only 21 (24%) were asymptomatic and all the latter had a toxocariasis. Among the 43 with an imported parasitic infection (schistosomiasis, filariasis, strongyloidiasis), only 4 (9%) were asymptomatic (schistosomiasis and strongyloidiasis, n=2 each).

At least one antiparasitic treatment was reported in all cases (**Figure 2**), in order of frequency: albendazole (n=84, 64%), ivermectin (n=52, 40%), praziquantel (n=32, 24%), flubendazole (n=6, 5%), diethylcarbamazine and triclabendazole (n=2 each, 2%). Eight patients (6%) had also received a treatment with corticosteroids: three of them had 1g solumedrol pulses and oral steroids thereafter, and 5 received oral systemic steroids (20 to 80mg/day equivalent prednisone).

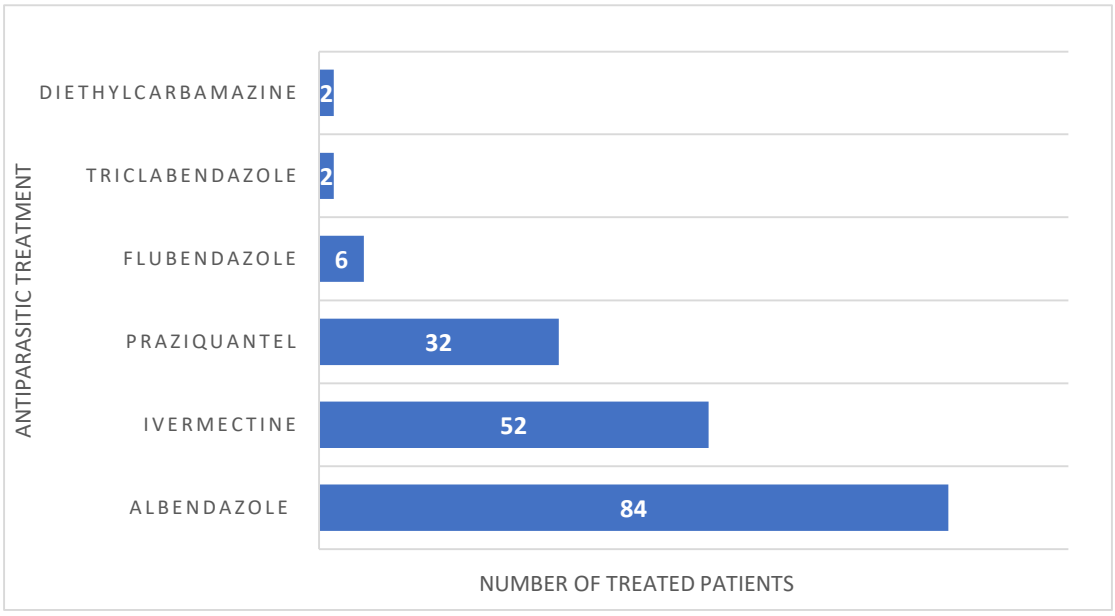

Figure 2. Antiparasitic treatment.

Table 3. Demographic, clinical and biological features: eosinophil-related organ involvement.

	All patients (N = 131)	Toxocariasis (N=73)	Schistosomiasis (N=25)	Filariasis (N=10)	Fascioliasis (N=9)	Strongyloidiasis (N=8)	Trichinosis (N=5)
Age at diagnosis, median (range), years	**50.7 (1.7-90.5)**	**63.9 (6.2-90.5)**	**25.5 (6.5-70.9)**	**36.1 (1.7-68.3)**	**63.7 (9.4-88.7)**	**39.1 (4.5-64.4)**	**63.8 (44.6-78.2)**
Male	**87 (66.4%)**	**50 (68.5%)**	**22 (88%)**	**4 (40%)**	**3 (33%)**	**5 (62.5%)**	**3 (60%)**
Contact with pets	**27 (19.8%)**	**16 (21.5%)**	**1 (4%)**	**3 (30%)**	**3 (33%)**	**2 (25%)**	**2 (40%)**
Allergic disorders	**31 (23.7%)**¥	**19 (26%)**	**1 (4%)**	**3 (30%)**	**3 (33%)**	**1 (12.5%)**	**3 (60%)**
Stay in endemic area	**69 (52.7%)**	**20 (27.4%)**	**25 (100%)**	**10 (100%)**	**2 (22%)**	**8 (100%)**	**4 (80%)**
AEC, median (IQR), x 10^9/L	**1.6 (1.1-3.0)**	**1.4 (1.0-2.7)**	**1.1 (0.8-3.0)**	**1.8 (1.2-3.0)**	**3.0 (2.0-4.0)**	**2.0 (1.6-3.3)**	**1.7 (1.3-8.0)**
Eosinophilia (0.5-1.5 x 10^9/L)	64 (48.9%)	39 (53.4%)	16 (64%)	4 (40%)	-	2 (25%)	2 (40%)
Hypereosinophilia (>1.5 x 10^9/L)	67 (51.1%)	34 (46.6%)	9 (36%)	6 (60%)	9 (100%)	6 (75.0%)	3 (60%)
Asymptomatic	**27 (20.6%)**	**23 (31.5%)**	**2 (8%)**	**-**	**-**	**2 (25.0%)**	**-**
EOSINOPHIL RELATED ORGAN INVOLVEMENT							
Skin	**44 (33.6%)**	**29 (33.7%)**	**2 (8%)**	**7 (70%)**	**4 (44%)**	**2 (25%)**	**2 (40%)**
Skin rash	23 (17.6%)	18 (24.7%)	1 (4%)	-	3 (33%)	1 (12.5%)	-
Urticaria	12 (9.2%)	7 (9.6%)	1 (4%)	2 (20%)	1 (11%)	1 (12.5%)	1 (20%)
Angioedema	12 (9.2%)	5 (6.8%)	1 (4%)	5 (50%)‡	-	-	1 (20%)
Digestive	**31 (23.7%)**¥	**11 (15.1%)**	**11 (44%)**	-	**5 (55%)**	**1 (12.5%)**	**2 (40%)**
Diarrhoea	15 (11.5%)	6 (8.2%)	8 (32%)	-	1 (11%)	1 (12.5%)	2 (40%)
Abdominal pain	11 (8.4%) ¥	3 (4.1%)	3 (12%)	-	4 (44%)	-	-
Biopsy-proven colitis*	2 (1.5%)	1 (1.4%)	1 (4%)	-	-	-	-
Icterus	1 (0.8%)	1 (1.4%)	-	-	-	-	-
Jejunitis†	1 (0.8%)	-	-	-	-	1 (12.5%)	-
Mesenteric panniculitis	1 (0.8%)	1 (1.4%)	-	-	-	-	-
Chylous ascites	1 (0.8%)	-	1 (4%)	-	-	-	-
Respiratory	**22 (16.8%)**	**13 (17.8%)**	**1 (4%)**	**2 (20%)**	**1 (11%)**	**3 (37.5%)**	**2 (40%)**
Dyspnoea and/or cough	10 (7.6%)	7 (9.6%)	1 (4%)	-	-	1 (12.5%)	1 (20%)
Bilateral pulmonary infiltrates†	7 (5.3%)	4 (5.4%)	-	1 (10%)	-	2 (37.5%)	-
Bronchospasm	4 (3.1%)	2 (2.7%)	-	1 (10%)	-	-	1 (20%)
Eosinophilic pleural effusion	1 (0.8%)	-	-	-	1 (11%)	-	-
Vascular	**7 (5.3%)**	**5 (6.8%)**	**1 (4%)**	**-**	-	-	**1 (20%)**
Venous thrombosis	7 (5.3%)	5 (6.8%)	1 (4%)	-	-	-	1 (20%)
Arterial thrombosis	1 (0.8%)	1 (1.4%)	-	-	-	-	-
Cardiac	**2 (1.5%)**	**1 (1.4%)**	**-**	**-**	**-**	**-**	**1 (20%)**
Myopericarditis	1 (0.8%)	-	-	-	-	-	1 (20%)
Endomyocardial fibrosis	1 (0.8%)	1 (1.4%)	-	-	-	-	-

Table 3 (continued). Demographic, clinical and biological features: parasite-related manifestations and other symptoms.

	All patients (N = 131)	Toxocariasis (N=73)	Schistosomiasis (N=25)	Filariasis (N=10)	Fascioliasis (N=9)	Strongyloidiasis (N=8)	Trichinosis (N=5)
PARASITE RELATED MANIFESTATIONS							
Haematuria	8 (6.1%)	-	8 (32%)	-	-	-	-
Liver abscess	5 (3.8%)	3 (4.1%)	1 (4%)	-	1 (11%)	-	-
Cutaneous *larva migrans*	2 (1.5%)	-	-	1 (10%)	-	1 (12.5%)	-
Ocular *larva migrans*	4 (3.1%)	-	-	4 (40%)	-	-	-
Uveitis	2 (1.5%)	2 (2.7%)	-	-	-	-	-
Occipital pseudo-tumour£	1 (0.8%)	-	1 (4%)	-	-	-	-
OTHER SYMPTOMS							
Muscular involvement	**6 (4.6%)**	**2 (2.7%)**	**-**	**1 (10%)**	**-**	**-**	**3 (60%)**
Myalgia	5 (3.8%)	1 (1.4%)	-	1 (10%)	-	-	3 (60%)
CK elevation	3 (2.3%)	1 (1.4%)	-	-	-	-	2 (40%)
Necrosing myositis	1 (0.8%)	1 (1.4%)	-	-	-	-	-
Constitutional symptoms	**10 (7.6%)**	**5 (6.8%)**	**3 (12%)**	**-**	**1 (11%)**	**1 (12.5%)**	**-**
Fever	7 (5.3%)	3 (4.1%)	2 (8%)	-	1 (11%)	1 (12.5%)	-
Weight loss	4 (3.1%)	3 (4.1%)	1 (4%)	-	-	-	-

CRP: C reactive protein; AEC: absolute eosinophil count; * With eosinophilic infiltrate; † Computed tomography scan finding; ‡ Corresponding to Calabar swelling for some authors; ¥ including the sole case of anisakidose.
£ With pathological evidence of the parasite.

Toxocariasis

Toxocariasis was the most common infection with 73 patients (56%) and a wide spectrum of Eo-R organ involvement. Sixteen (22%) reported a contact with a domestic dog or cat. Cutaneous symptoms were the most frequent (n=29, 34%), mainly rash (n=18, 25%), urticaria (n=7, 10%) or angioedema (n=5, 7%). Respiratory involvement occurred in 13 patients (18%): 7 patients (10%) had dyspnoea and/or cough, 4 patients (5%) bilateral pulmonary infiltrates, 2 patients (3%) bronchospasm. Gastrointestinal involvement was reported in 11 patients (15%), 6 (8%) presented diarrhoea and 3 abdominal pain (4%), there was one case of biopsy proven eosinophilic colitis, one case of icterus and one case of mesenteric panniculitis. Vascular involvement was found in 5 patients (7%), mainly venous thrombosis (n=5, 7%), and one case of arterial thrombosis. Endomyocardial fibrosis was identified in one patient. Myalgias were also noted in two patients, one of whom had necrotizing myositis. Considering Pa-R symptoms, ocular toxocariasis was found in two cases and liver abscesses in 3 cases. Finally, 23 (32%) patients were asymptomatic. (See **Supplementary Table 6** for detailed information).

Other helminthiases

Schistosomiasis (n=25). All patients had stayed in endemic area in Africa and in 14 cases, the parasite was detected in the stool and/or urine. Digestive involvement was found in n=11 (44%). Cutaneous symptoms were relatively uncommon (n=2, 8%), as well as respiratory involvement (1 patient with cough and dyspnoea). Pa-R manifestations were the following: 8 cases of macroscopic haematuria, one case of liver abscess and one of cerebral pseudo-tumour located in the occipital region (*Schistosoma haematobium* was identified on the resection piece). Three patients (2%) presented constitutional symptoms: 2 had fever and one reported weight loss. (**Supplementary Table 7**). We included in our

study a case of cerebral schistosomiasis, previously published by Loridant et al. (53) and revealed by a homonymous lateral hemianopia initially suspected to be a glioblastoma. The diagnosis was established by extemporaneous pathological examination and the incriminated species was *Schistosomia haematobium* with an associated intestinal location.

Filariasis (n=10). Skin manifestation occurred in 70% of patients with 5 cases (50%) of remitting limb oedema (also known as Calabar swelling), 2 cases of urticaria (20%). Two patients showed respiratory involvement: one had bilateral pulmonary infiltrates, the other one bronchospasm. Ocular *larva migrans* was the most frequent Pa-R manifestation, observed in n=4 (40%), and one case of cutaneous *larva migrans* was also recorded (**Supplementary Table 8**).

Fascioliasis (n=9). The main Eo-R manifestations were digestive (n=5) and unspecific (diarrhoea, abdominal pain), followed by skin manifestations (n=4): 3 cases of skin rash and one of urticaria. Eosinophilic pleural effusion was observed in one case. The sole Pa-R manifestation was a liver abscess (n=1). (**Supplementary Table 9**)

Strongyloidiasis (n=8). Respiratory involvement was documented in n=3 (2 cases of bilateral pulmonary infiltrates and 1 of severe dyspnoea), skin involvement in n=2 (one rash and one urticaria). There was one case of cutaneous *larva migrans*. (**Supplementary Table 10**)

Trichinosis (n=5). Skin involvement was documented in n=2 (one case of angioedema and one of urticaria), diarrhoea in n=2, respiratory manifestations in 2 cases (of which one of bronchospasm). There was one case of myopericarditis and venous thrombosis. Myalgias were present in n=3 and CK elevation in n=2. (**Supplementary Table 11**)

Anisakiasis. The sole reported case of Anisakiasis involved an 8-year-old girl with persistent abdominal pain associated with a 4.4 x 10^9/L HE. After treatment with Albendazole, both the symptoms and the circulating HE resolved.

AEC and CRP levels

The median AEC value was higher in symptomatic patients than in asymptomatic ones (1.7 [IQR 1.0-4.0] vs. 1.2 [IQR 1.1-1.7] x 10^9/L; p=0.037). The graphical representation of AEC according to parasitosis (**Figure 3**) highlights that median AEC is above 1.5 x 10^9/L for filariasis, fascioliasis, strongyloidiasis and trichinosis and below this threshold for toxocariasis and schistosomiasis. We further notice that all fascioliasis presented an HE and that major HE (above 10 x 10^9/L) is particularly found in toxocariasis.

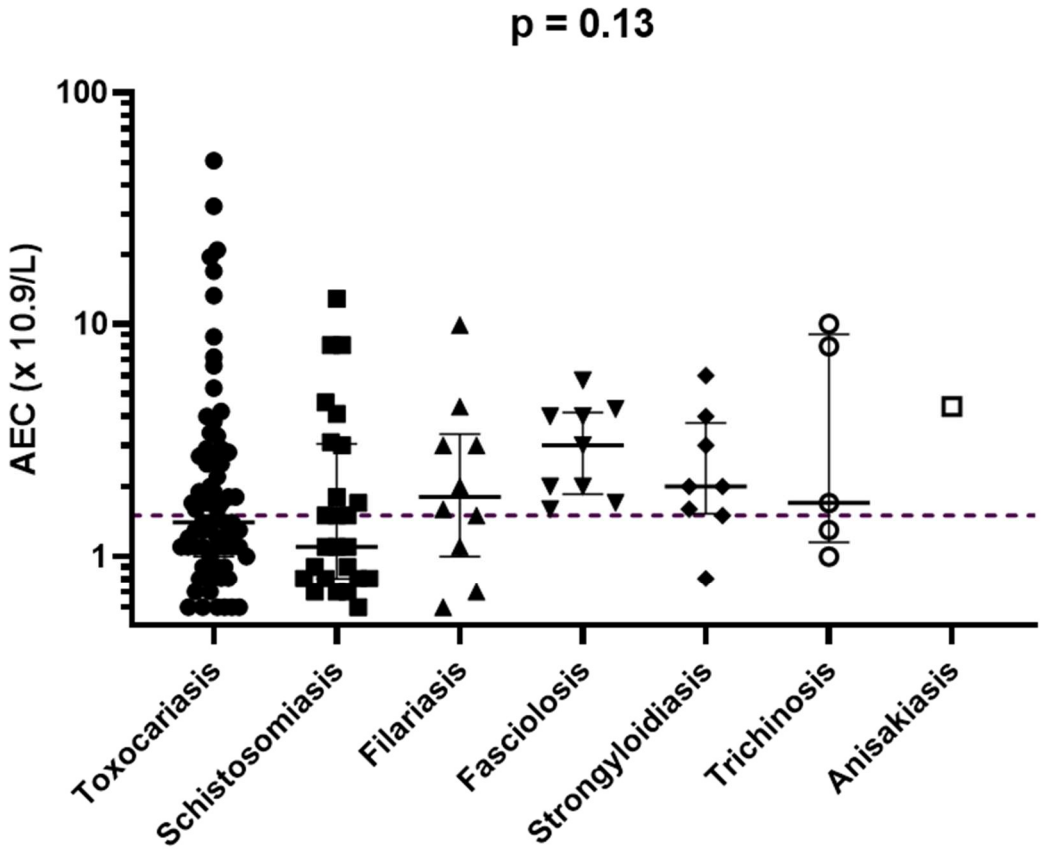

Figure 3. AEC distribution for each parasitosis.
AEC: Absolute Eosinophil Count (x 10^9/L). Dotted line: 1.5 x 10^9/L.

There was no statistically significant difference for CRP (6 [IQR 1.5-20.5] mg/L in symptomatic patients vs. 7 [IQR 1.5-20.0] mg/L in asymptomatic patients; p=0.537).

AEC and organ involvement

AEC were different according to the organ involvement, with an increasing level between patients with skin, respiratory, digestive, vascular and cardiac involvements (p = 0.0057) (**Figure 4**). However, there was no statistically significant difference in a post hoc 2-to-2 comparison according to Dunn's test.

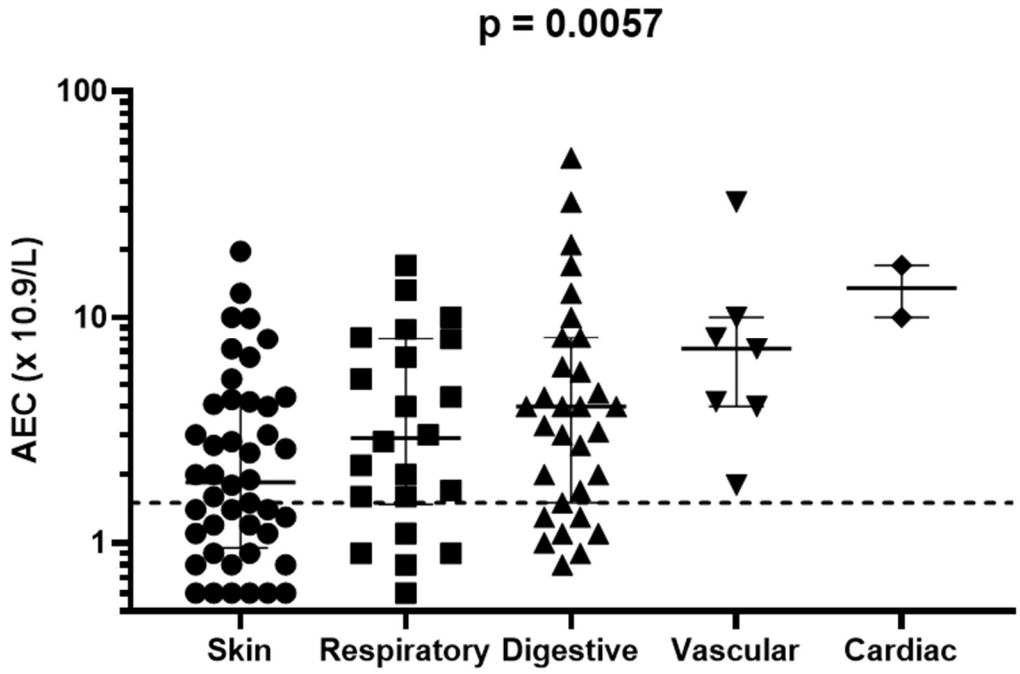

Figure 4. AEC distribution for each organ involvement.
AEC: Absolute Eosinophil Count (x 10^9/L). Dotted line: 1.5 x 10^9/L.

Furthermore, AEC increased when we compared patients without any Eo-R involvement (n=47/131, 36%), patients with one organ involvement, i.e a single-organ reactive HES (n=67/131, 51%) and patients with at least 2 organ involvements, i.e a system HES (n=17/131, 13%) (p<0.0001) (**Figure 5**).

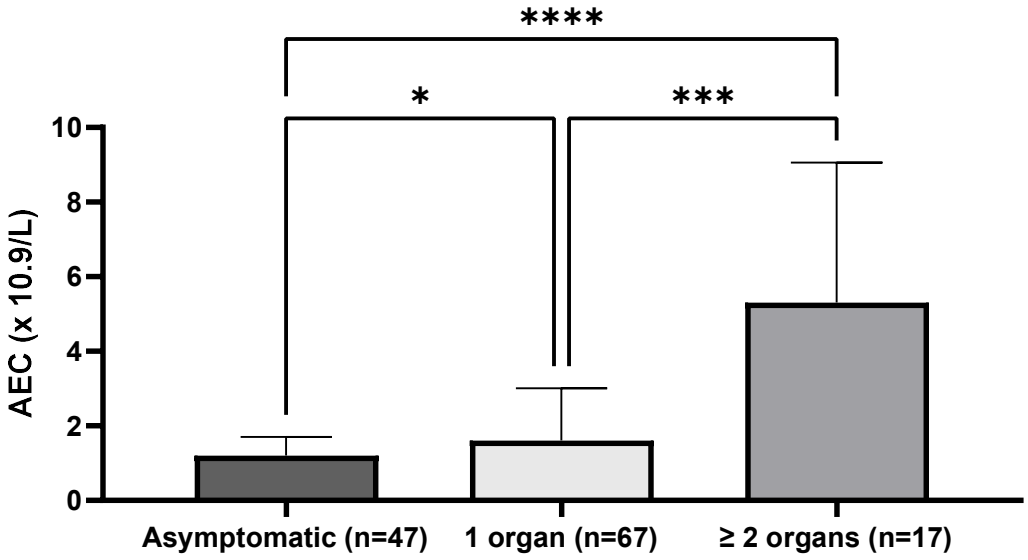

Figure 5. AEC comparison between asymptomatic patients (n=47), single organ-involvement (n=67) and multi-organ involvement (n=17).
p-value (Kruskal-Wallis test): * < 0.05; *** < 0.001; **** < 0.0001. AEC: Absolute Eosinophil Count (x 10^9/L).

Comparison of clinical pattern of Eo-R organ manifestations in helminthiasis and idiopathic HES

Finally, we aimed to assess if Eo-R organ involvements in helminthiasis differed from organ involvements observed in idiopathic HES patients. We compared the clinical pattern of patients with Eo-R manifestations and AEC > 1.5 x 10^9/L (n=52), with idiopathic HES patients from a national cohort (n=148) (**Figure 6**). There was no statistically significant difference (p>0.05) between the two cohorts in the frequency of cutaneous (48% of helminthiasis vs. 42% of iHES), gastrointestinal (44% vs. 39%), respiratory (33% vs. 32%), and vascular (14% vs. 12%) involvement. However, cardiac involvement was significantly more frequent in iHES: 30% versus 4% in helminthic infections (p=0.0023).

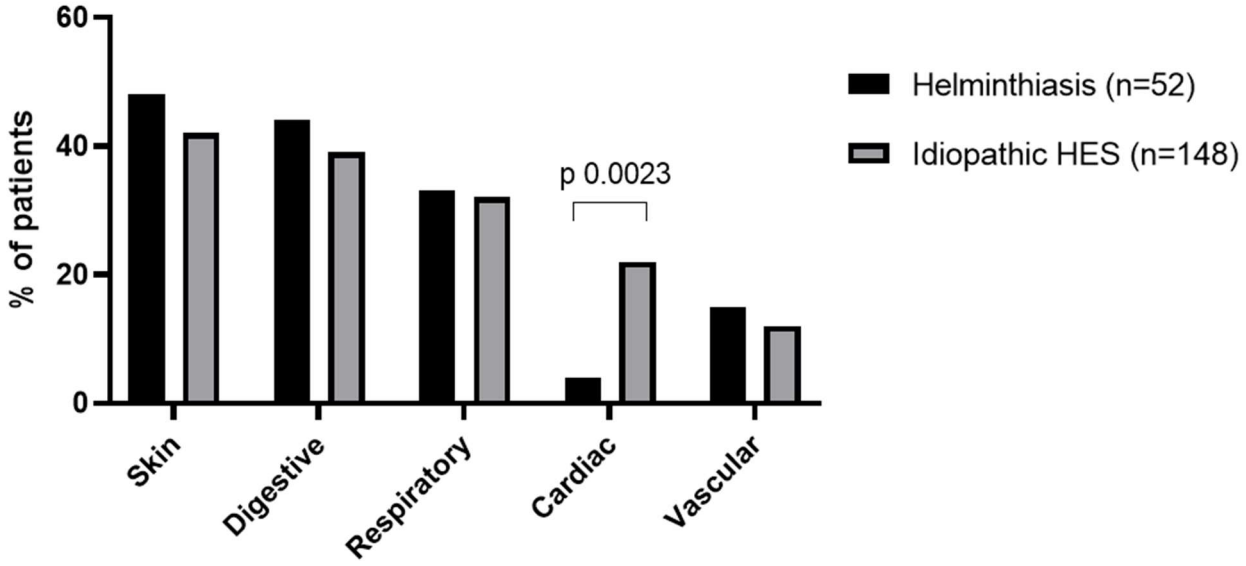

Figure 6. Comparison of clinical features between helminthiasis and iHES.
Unsignificant differences (p>0.05) were found for skin, digestive respiratory and vascular involvement. The iHES group included 148 patients of a national cohort, and the helminthiases group involved the 52 patients with an AEC > 1.5 x 10^9/L and Eo-R manifestations.

DISCUSSION

Our study aimed to describe the spectrum of Eo-R organ damages in patients who were diagnosed with a helminthiasis with eosinophilia in a university hospital in North of France. The main autochthonous parasitic infection was toxocariasis by far, and the main supposed imported parasitic infection was schistosomiasis. In one hand, our study also shows that one fifth of the whole population and that one third of patients with toxocariasis were asymptomatic despite eosinophilia or hypereosinophilia, but in a second hand, that Eo-R symptoms in the other patients are similar to idiopathic HES, excepted cardiac involvement which was less frequent.

To distinguish Eo-R from Pa-R symptoms, we considered as probable Eo-R symptoms the usual symptoms seen in other eosinophilic disorders, and which could not be directly induced by the parasite. However, this assumed bias must be discussed for some of them. For example, digestive symptoms could be induced by an adult worm, but blood eosinophilia (which was an inclusion criteria) is usually absent at this stage of the infection, conversely to mucosal eosinophilia which can contribute to symptoms. Calabar swelling are transient oedema of the limbs, sometimes highly pruritic and painful, and are considered as pathognomonic of *Loa loa* filariasis by some authors (32). However, similar recurrent angioedema or oedema were observed in other helminthiasis in our case series, and are also well known features of lymphocytic and idiopathic HES (33). In contrast, conjonctival *larva migrans* (toxacariasis, filariasis...) or cutaneous *larva migrans* (hookworm, filariasis…), macroscopic haematuria or bladder calcifications (Strongyloidiasis) are certain Pa-R symptoms that can lead to a quick diagnosis in a context of eosinophilia.

The clinical manifestations associated with toxocariasis were extremely diverse: from asymptomatic infection to severe organ injury, sometimes mimicking a systemic disease (34). The high frequency of asymptomatic infection rises the need to search toxocariasis in patients with eosinophilia, even if the patient does not report any contact with dogs or cats (only 21.5% did in our case series). The underlying issue under this high frequency, is that a confirmed anti-toxocara antibody test does not mean that infection is recent and/or responsible of eosinophilia. Indeed, a recent systematic review and meta-analysis reported seroprevalence estimates for toxocariasis at 19% (CI95%: 16.6–21.4) and European regions had the lower seroprevalence, estimated at 10.5% (8.5–12.8) (35). Of course, a large majority of cases are asymptomatic and may not develop eosinophilia and Eo-R symptoms, and a single positive titre indicates that a person has had contact with *Toxocara spp* in the past, it cannot distinguish between active infection and a serological scar. Therefore, for toxocariasis-related eosinophilia, we here considered a definite diagnosis when no other explanation was found for eosinophilia, and when anti-parasitic drug seemed to be efficient, with persistent clinical remission and normalization of AEC (out of any steroid treatments).

Another side of the diagnostic challenge in helminthic infections is the delay between parasitic infection and blood EO. Low in the invasion stage, the circulating EO increases rapidly with tissue migration of the parasite and progressively decreases after a state phase. The blood EO evolution according to the time follows an asymmetric bell curve (known as Lavier's curve in French-speaking countries) possibly recurring in case of reinfection. As a consequence of this delay, when blood EO and Eo-R symptoms occur, the period in which the parasite could be directly detected is over. This could explain the low diagnostic reliability of repeated parasitological stool examinations in clinical practice.

In toxocariasis cases, skin, respiratory and digestive symptoms were the most frequent. Skin symptoms were unspecific: skin rash, urticaria or angioedema, which are common features of idiopathic HES, should evoke the diagnosis of toxocariasis, as reported by others (36). A few studies suggest an association between chronic urticaria and infection or exposure to this parasite (37,38), sometimes resolving after treatment with albendazole (39). We also observed a case of necrotizing myositis, a rare but known complication (40–42) of toxocariasis (although often associated with a *Staphyloccocus aureus* infection, which was not the case here). Abdominal symptoms are a typical complain of Toxocariasis, the presence of liver abscesses is not uncommon (43,44) and occurred in 3 patients, sometimes masquerading metastasis or liver malignancy (45) responding to antiparasitic drugs for two of our patients (data not available for the third one).

A supplementary analysis was conducted in toxocariasis patients, comparing Eo-R manifestations according to AEC levels (below and above 1.5 x 10^9/L). The excluded patients due to the absence of EO (AEC under 0.5 x 10^9/L) were used as control group (among the 42 patients without EO, 38 were toxocariasis). The comparison showed two facts (see **Supplementary Table 12**). First, that extracutaneous manifestations appear when AEC is greater than 0.5 x10^9/L. Secondly, that among cutaneous manifestations, skin rash seems to be more related to eosinophils than angioedema/urticaria. However, the links between urticaria and an incidentally detected positive toxocariasis serology remains unclear (36,38) and blood eosinophilia does not always reflect cutaneous eosinophilic infiltration (46).

In other parasitic infections, Eo-R were also more frequent that Pa-R symptoms. We particularly highlight the frequency of cardiac and vascular complications during helminthiasis, occurring in 8 patients or 11% of the cohort, including 7 cases of venous thrombosis and one of arterial thrombosis, one case of myopericarditis and one of

endomyocardial fibrosis. Around 30 cases of myocarditis, pericarditis and/or endomyocardial fibrosis have been reported with toxocariasis and numerous others with tropical helminthiasis, mainly schistosomiasis, cysticercosis, or echinococcosis (47–50). HE greater than 1.5 x 10^9/L is always reported in these cases, as in our 2 cases, but authors suggest that myocardial damages could be made by both local infection by larva and by local eosinophil-mediated hypersensitivity reactions (48,50). Venous thrombotic events (n=7 in our case series) were rarely reported, but also only with HE > 1.5 x 10^9/L. The scientific literature reports arterial thrombotic manifestations during toxocariasis in only one case, with the presence of an intra-aortic thrombus (which was also the case in our patients): the mechanism suggested by Traboulsi and al. is that of an immune reaction related to parasite migration, rather than eosinophils themselves despite a major HE with an AEC at 15 x 10^9 /L (51).

Finally, when all parasitic infections were considered, AEC were also different according to the organ involvement, with an increasing level between patients with skin, respiratory, digestive, vascular and cardiac involvements ($p = 0.0057$) (**Figure 4**), and AEC increased when comparing patients without any Eo-R involvement, with one organ involvement, or with at least 2 organ involvements ($p < 0.0001$) (**Figure 5**): this highlights once again that eosinophils may be responsible of severe reactive HES manifestations, and that higher AEC may expose patients to a more systemic disease.

Comparison of clinical features between helminthiasis and iHES showed similar frequencies for cutaneous, gastro-intestinal, respiratory and vascular involvements, but not cardiac involvement which appeared more frequent in the iHES cohort. This similarity highlights that an idiopathic HES must not be diagnosed without a complete parasitic investigations and that anti-parasitic drug should be considered (54).

Our study had the following strengths: we included 131 patients with 7 different helminthiases through serological screening combined with confirmation test and/or clinical and biological criteria to increase the diagnostic reliability. We described the clinical features of the different parasitic infection making a distinction between Eo-R manifestations and Pa-R symptoms. Finally, the comparison between our helminthiasis cohort and the iHES COHESion cohort highlights a similar clinical profile (except for cardiac involvement). However, our work was limited by its retrospective character and a collection bias with the exclusion of many patients with incomplete data.

CONCLUSION

Ce travail a permis de décrire les helminthiases les plus fréquemment diagnostiquées dans un CHU de France métropolitaine. Parmi les 131 patients inclus, on comptait une majorité de toxocaroses (n=73), 25 cas de bilharziose, 10 de filariose, 9 de distomatose, 8 d'anguillulose, 5 de trichinose et un d'anisakidose. Les quinze patients atteints de possible ascaridiose n'ont finalement pas été inclus dans notre étude en raison de la faible spécificité de la sérologie (nombreuses réactions croisées avec d'autres helminthiases) et d'une clinique peu spécifique rendant la confirmation diagnostique complexe (55,56). Deux catégories de symptômes était distinguées : ceux associés à l'éosinophile (par analogie avec les syndromes hyperéosinophiliques) et ceux directement liés à la présence du parasite (*larva migrans* cutané ou oculaire, abcès hépatiques, toxocarose oculaire, ou localisation parasitaire cérébrale). Cette distinction a permis de faire émerger des manifestations communes aux différentes parasitoses, attribuées à une toxicité de l'éosinophile : cutanées (avec les angiocœdèmes récidivant de la loase ou de la trichinose; l'urticaire de la toxocarose et d'autres éruptions cutanées), digestive (diarrhées et douleurs abdominales, colite à éosinophile…), respiratoires (infiltrats pulmonaires bilatéraux, bronchospasme), vasculaire (majoritairement des thromboses veineuses) et cardiaques (fibrose endomyocardique et myopéricardite).

Nous avons plus particulièrement discuté l'association avec l'éosinophile de deux types de manifestations. D'abord, l'urticaire chronique décrite dans la toxocarose, pour certains auteurs attribuable à un mécanisme d'hypersensibilité (36,38,57), pour d'autre secondaire à une infiltrat éosinophilique cutané (58). La même question se posait pour les manifestations thrombotiques, dont la fréquence est comparable dans l'éosinophilie parasitaires et dans les SHE idiopathique. L'étude récemment menée par Réau et coll. sur les thromboses veineuse au cours des maladies associées aux éosinophilies incluait

plusieurs patients atteints de parasitoses (59). Sur le plan physiopathologique, le caractère thrombotique de l'éosinophilie circulante est soutenu par plusieurs études : en lien avec la dégranulation mastocytaire (60), la formation de complexes immuns circulants (61), l'expression du facteur tissulaire secondaire à l'élévation des taux sériques d'IL-1, d'IL-6 et de TNF alpha (62,63).

Notre étude était limitée par la difficulté du diagnostic parasitologique. Tout d'abord en raison de la faible spécificité des tests sérologiques de dépistage avec de nombreuses faux positifs et l'absence de tests de confirmation pour certaines parasitoses. Par ailleurs, le décalage entre la phase d'excrétion du parasite et l'éosinophilie circulante illustré par la courbe de Lavier rend particulièrement peu rentable l'examen parasitologique des selles chez le patient adressé pour une éosinophilie.

Au final, ce travail a permis d'étudier de façon globale les manifestations cliniques associées aux éosinophilies parasitaires. La proximité du profil clinique des parasitoses avec les SHE idiopathique insiste sur le rôle pathogène de l'éosinophile et invite à rapprocher l'éosinophilie associée aux parasitoses à l'ensemble des maladies associées aux éosinophiles.

BIBLIOGRAPHIE

1. Zacharski LR, Elveback LR, Kinman JW. Leukocyte counts in healthy adults. Am J Clin Pathol. 1971 Aug;56(2):148–50.

2. van Assendelft OW. Reference values for the total and differential leukocyte count. Blood Cells. 1985;11(1):77–96.

3. Butt NM, Lambert J, Ali S, Beer PA, Cross NCP, Duncombe A, et al. Guideline for the investigation and management of eosinophilia. British Journal of Haematology. 2017;176(4):553–72.

4. Causes and outcomes of hypereosinophilia in a tropical country. Asian Pac J Allergy Immunol [Internet]. 2021 [cited 2021 Jul 5]; Available from: https://apjai-journal.org/wp-content/uploads/2021/04/AP-221220-1021.pdf

5. O'Connell EM, Nutman TB. Eosinophilia in Infectious Diseases. Immunol Allergy Clin North Am. 2015 Aug;35(3):493–522.

6. Gazzinelli-Guimaraes PH, Nutman TB. Helminth parasites and immune regulation. F1000Res. 2018 Oct 23;7:1685.

7. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. J Clin Invest. 2008 Apr 1;118(4):1311–21.

8. Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018 Jan 20;391(10117):252–65.

9. Wilder HC. Nematode endophthalmitis. Nematode endophthalmitis [Internet]. 1950 [cited 2021 Oct 12]; Available from: https://www.cabdirect.org/cabdirect/abstract/19500800832

10. Macpherson CNL. The epidemiology and public health importance of toxocariasis: A zoonosis of global importance. International Journal for Parasitology. 2013 Nov 1;43(12):999–1008.

11. Despommier D. Toxocariasis: Clinical Aspects, Epidemiology, Medical Ecology, and Molecular Aspects. Clinical Microbiology Reviews. 2003 Apr 1;16(2):265–72.

12. Taylor MRH, Keane CT, O'connor P, Anthony Girdwood RW, Smith H. Clinical Features of Covert Toxocariasis. Scandinavian Journal of Infectious Diseases. 1987 Jan 1;19(6):693–6.

13. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014 Jun 28;383(9936):2253–64.

14. Lambertucci JR, Drummond SC, Voieta I, de Queiróz LC, Pereira PPN, Chaves BA, et al. An Outbreak of Acute Schistosoma mansoni Schistosomiasis in a Nonendemic Area of Brazil: A Report on 50 Cases, Including 5 With Severe Clinical Manifestations. Clinical Infectious Diseases. 2013 Jul 1;57(1):e1–6.

15. Molyneux D. Lymphatic Filariasis (Elephantiasis) Elimination: A public health success and development opportunity. Filaria J. 2003 Sep 9;2:13.

16. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. Trans R Soc Trop Med Hyg. 2008 Oct;102(10):983–9.

17. Murdoch ME, Asuzu MC, Hagan M, Makunde WH, Ngoumou P, Ogbuagu KF, et al. Onchocerciasis: the clinical and epidemiological burden of skin disease in Africa. Ann Trop Med Parasitol. 2002 Apr;96(3):283–96.

18. Hopkins A. Onchocerciasis then and now: achievements, priorities and challenges. Community Eye Health. 2017;30(100):92–5.

19. Peters L, Burkert S, Grüner B. Parasites of the liver – epidemiology, diagnosis and clinical management in the European context. Journal of Hepatology. 2021 Jul 1;75(1):202–18.

20. Gottstein B, Pozio E, Nöckler K. Epidemiology, Diagnosis, Treatment, and Control of Trichinellosis. Clinical Microbiology Reviews. 2009 Jan 1;22(1):127–45.

21. Ozdemir D, Ozkan H, Akkoc N, Onen F, Gurler O, Sari I, et al. Acute trichinellosis in children compared with adults. Pediatr Infect Dis J. 2005 Oct;24(10):897–900.

22. Yasunaga H, Horiguchi H, Kuwabara K, Hashimoto H, Matsuda S. Clinical Features of Bowel Anisakiasis in Japan. Am J Trop Med Hyg. 2010 Jul;83(1):104–5.

23. Nieuwenhuizen NE. Anisakis - immunology of a foodborne parasitosis. Parasite Immunol. 2016 Sep;38(9):548–57.

24. Yoon S-Y, Baek S, Park SY, Shin B, Kwon H-S, Cho YS, et al. Clinical course and treatment outcomes of toxocariasis-related eosinophilic disorder. Medicine (Baltimore). 2018 Sep 14;97(37):e12361.

25. Kwon N-H, Oh M-J, Lee S-P, Lee B-J, Choi D-C. The prevalence and diagnostic value of toxocariasis in unknown eosinophilia. Ann Hematol. 2006 Apr;85(4):233–8.

26. Salas-Coronas J, Cabezas-Fernández MT, Vázquez-Villegas J, Soriano-Pérez MJ, Lozano-Serrano AB, Pérez-Camacho I, et al. Evaluation of eosinophilia in immigrants in Southern Spain using tailored screening and treatment protocols: A prospective study. Travel Med Infect Dis. 2015 Aug;13(4):315–21.

27. Van Den Broucke S, Kanobana K, Polman K, Soentjens P, Vekemans M, Theunissen C, et al. Toxocariasis Diagnosed in International Travelers at the Institute of Tropical Medicine, Antwerp, Belgium, from 2000 to 2013. PLoS Negl Trop Dis. 2015 Mar 6;9(3):e0003559.

28. Khoury P, Grayson PC, Klion AD. Eosinophils in vasculitis: characteristics and roles in pathogenesis. Nat Rev Rheumatol. 2014 Aug;10(8):474–83.

29. Mitre E, Klion AD. Eosinophils and helminth infection: protective or pathogenic? Semin Immunopathol. 2021 Jun;43(3):363–81.

30. Magnaval JF, Fabre R, Maurières P, Charlet JP, de Larrard B. Application of the western blotting procedure for the immunodiagnosis of human toxocariasis. Parasitol Res. 1991;77(8):697–702.

31. Valent P, Klion AD, Horny H-P, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. Journal of Allergy and Clinical Immunology. 2012 Sep 1;130(3):607-612.e9.

32. Nutman TB, Miller KD, Mulligan M, Ottesen EA. Loa loa infection in temporary residents of endemic regions: recognition of a hyperresponsive syndrome with characteristic clinical manifestations. J Infect Dis. 1986 Jul;154(1):10–8.

33. Abisror N, Mekinian A, Dechartres A, Groh M, Berezne A, Noel N, et al. Abnormal T-cell phenotype in episodic angioedema with hypereosinophilia (Gleich's syndrome): frequency, clinical implication and prognosis. J Am Acad Dermatol. 2019 Feb 6;S0190-9622(19)30196-3.

34. Rubinsky-Elefant G, Hirata CE, Yamamoto JH, Ferreira MU. Human toxocariasis: diagnosis, worldwide seroprevalences and clinical expression of the systemic and ocular forms. Ann Trop Med Parasitol. 2010 Jan;104(1):3–23.

35. Rostami A, Ma G, Wang T, Koehler AV, Hofmann A, Chang BCH, et al. Human toxocariasis - A look at a neglected disease through an epidemiological 'prism'. Infect Genet Evol. 2019 Oct;74:104002.

36. Gavignet B, Piarroux R, Aubin F, Millon L, Humbert P. Cutaneous manifestations of human toxocariasis. Journal of the American Academy of Dermatology. 2008 Dec 1;59(6):1031–42.

37. Matos Fialho PM, Correa CRS, Lescano SZ. Seroprevalence of Toxocariasis in Children with Urticaria: A Population-based Study. J Trop Pediatr. 2017 Oct 1;63(5):352–7.

38. Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites – a systematic review. Allergy. 2016;71(3):308–22.

39. Kim M-H, Jung J-W, Kwon J-W, Kim T-W, Kim S-H, Cho S-H, et al. A case of recurrent toxocariasis presenting with urticaria. Allergy Asthma Immunol Res. 2010 Oct;2(4):267–70.

40. Bellanger A-P, Runge M, Wendling D, Humbert P. Lumbar myositis associated with Toxocara spp. infection. Reumatol Clin. 2014 Jan 1;10(1):54–5.

41. Walsh SS, Robson WJ, Hart CA. Acute transient myositis due to Toxocara. Arch Dis Child. 1988 Sep;63(9):1087–8.

42. Lambertucci JR, Rayes A, Serufo JC, Teixeira DM, Gerspacher-Lara R, Nascimento E, et al. Visceral larva migrans and tropical pyomyositis: a case report. Rev Inst Med Trop Sao Paulo. 1998 Dec;40(6):383–5.

43. Ramachandran J, Chandramohan A, Gangadharan SK, Unnikrishnan LS, Priyambada L, Simon A. Visceral larva migrans presenting as multiple liver abscesses. Trop Doct. 2013 Oct;43(4):154–7.

44. Ha KH, Song JE, Kim BS, Lee CH. Clinical characteristics and progression of liver abscess caused by toxocara. World J Hepatol. 2016 Jun 28;8(18):757–61.

45. Park S, Kim YS, Kim YJ, Kyung SY, Park J-W, Jeong SH, et al. Toxocariasis masquerading as liver and lung metastatic nodules in patents with gastrointestinal cancer: clinicopathologic study of five cases. Dig Dis Sci. 2012 Jan;57(1):155–60.

46. Radonjic-Hoesli S, Brüggen M-C, Feldmeyer L, Simon H-U, Simon D. Eosinophils in skin diseases. Semin Immunopathol. 2021;43(3):393–409.

47. Enko K, Tada T, Ohgo KO, Nagase S, Nakamura K, Ohta K, et al. Fulminant eosinophilic myocarditis associated with visceral larva migrans caused by Toxocara canis infection. Circ J. 2009 Jul;73(7):1344–8.

48. Kuenzli E, Neumayr A, Chaney M, Blum J. Toxocariasis-associated cardiac diseases—A systematic review of the literature. Acta Tropica. 2016 Feb;154:107–20.

49. Park S-J, Jang C-W, Kim Y-K, Seo Y-H, Kim K-H, Kwon T-G, et al. Toxocariasis-Associated Acute Perimyocarditis with Cardiogenic Shock: A Case Report. Am J Case Rep. 2021 May 27;22:e930573-1-e930573-5.

50. Nunes MCP, Guimaraes Junior MH, Diamantino AC, Gelape CL, Ferrari TCA. Cardiac manifestations of parasitic diseases. Heart. 2017 May;103(9):651–8.

51. Traboulsi R, Boueiz A, Kanj SS. Catastrophic aortic thrombosis due to Toxocara infection. Scand J Infect Dis. 2007;39(3):283–5.

52. Maino A, Rossio R, Cugno M, Marzano AV, Tedeschi A. Hypereosinophilic syndrome, Churg-Strauss syndrome and parasitic diseases: possible links between eosinophilia and thrombosis. Curr Vasc Pharmacol. 2012 Sep;10(5):670–5.

53. Loridant S, Mouahid G, Cornu M, Allienne J-F, Leroy J, Maurage C-A, et al. Case Report: Hemianopia: From Suspected Glioblastoma to the Diagnosis of Ectopic Schistosomiasis Haematobium Infection in a Traveler Returning from the Republic of the Congo. Am J Trop Med Hyg. 2018 Jul;99(1):94–6.

54. Kahn JE, Groh M, Lefèvre G. (A Critical Appraisal of) Classification of Hypereosinophilic Disorders. Frontiers in Medicine. 2017;4:216.

55. Yoshida A, Kikuchi T, Nakagaki S, Maruyama H. Optimal ELISA antigen for the diagnosis of Ascaris suum infection in humans. Parasitol Res. 2016 Dec;115(12):4701–5.

56. Fillaux J, Magnaval J-F. Laboratory diagnosis of human toxocariasis. Veterinary Parasitology. 2013 Apr 15;193(4):327–36.

57. Pinelli E, Aranzamendi C. Toxocara infection and its association with allergic manifestations. Endocr Metab Immune Disord Drug Targets. 2012 Mar;12(1):33–44.

58. Mochizuki M, Bartels J, Mallet AI, Christophers E, Schröder JM. IL-4 induces eotaxin: a possible mechanism of selective eosinophil recruitment in helminth infection and atopy. J Immunol. 1998 Jan 1;160(1):60–8.

59. Réau V, Vallée A, Terrier B, Plessier A, Abisror N, Ackermann F, et al. Venous thrombosis and predictors of relapse in eosinophil-related diseases. Sci Rep. 2021 Mar 18;11:6388.

60. Tedeschi A, Kolkhir P, Asero R, Pogorelov D, Olisova O, Kochergin N, et al. Chronic urticaria and coagulation: pathophysiological and clinical aspects. Allergy. 2014 Jun;69(6):683–91.

61. Woerly G, Roger N, Loiseau S, Dombrowicz D, Capron A, Capron M. Expression of CD28 and CD86 by human eosinophils and role in the secretion of type 1 cytokines (interleukin 2 and interferon gamma): inhibition by immunoglobulin a complexes. J Exp Med. 1999 Aug 16;190(4):487–95.

62. Levi M, van der Poll T. Two-way interactions between inflammation and coagulation. Trends Cardiovasc Med. 2005 Oct;15(7):254–9.

63. Walsh GM, Hartnell A, Wardlaw AJ, Kurihara K, Sanderson CJ, Kay AB. IL-5 enhances the in vitro adhesion of human eosinophils, but not neutrophils, in a leucocyte integrin (CD11/18)-dependent manner. Immunology. 1990 Oct;71(2):258–65.

Table 4. Patients without eosinophilia (AEC < 0.5 x 10^9/L)

	N = 42
Age at diagnosis, median (range), years	54.3 (13.9-78.5)
Male	24 (57.1%)
Contact with pets	11 (26.2%)
Allergic disorders	17 (40.5%)
Stay in endemic area	8 (19.0%)
Glucocorticoids	3 (7.1%)
AEC, median (IQR), x 10^9/L	0.2 (0.1-0.3)
Parasitological diagnosis	
Toxocariasis	*38*
Asymptomatic	13
Urticaria	13
Angioedema	8
Skin rash	1
Uveitis	3
Cough	1
Fasciolosis: one case with cough, icterus and weight loss	
Trichinosis: one case with myalgia	
Schistosomiasis : one asymptomatic case	
Strongyloidiasis: one asymptomatic case	

AEC: absolute eosinophil count.

Table 5. Alternative diagnosis (other than helminthiasis)	N = 36
ABPA	4
AERD	1
Bullous pemphigoid	3
EGPA	2
Eosinophilic fasciitis	1
IgG4-related disease	1
Idiopathic Hypereosinophilic syndrome	3
Kounis syndrome	1
Leukaemias	
Acute myeloid leukaemia	2
Chronic eosinophilic leukaemia	1
Plasma cell leukaemia	1
Lymphomas	
Hodgkin lymphoma	1
Non Hodgkin lymphoma	3
Myelodysplastic syndrome	3
Myeloproliferative syndrome	2
Pembrolizumab induced eosinophilia	7

EGPA: eosinophilic granulomatosis with polyangiitis;
ABPA: allergic bronchopulmonary aspergillosis;
AERD: aspirin exacerbated respiratory disease (Widal or Samter's triad)

Table 6. Toxocariasis: Demographic, clinical, and biological features

	N = 73
Age at diagnosis, median (range), years	**63.9 (6.2-90.5)**
Adults	68 (93.2%)
Under 18 years old	5 (6.8%)
Male	50 (68.5%)
Contact with pets	**16 (21.5%)**
Allergic disorders	**19 (26%)**
Stay in endemic area	**20 (27.4%)**
Antiparasitic treatment	
Albendazole	63 (86.3%)
Flubendazole	4 (5.5%)
Ivermectin	20 (27.4%)
Praziquantel	2 (2.7%)
Antiparasitic treatment duration, median (range), days	**10 (1-15)**
Glucocorticoids use	**3 (4.1%)**
AEC, median (IQR), x 10^9/L	**1.4 (1.0-2.7)**
Eosinophilia (0.5-1.5 x 10^9/L)	39 (53.4%)
Hypereosinophilia (>1.5 x 10^9/L)	34 (46.6%)
CRP, median (IQR), mg/l	**8.5 (1.5-19.8)**
CRP > 5 mg/l	36 (49.3%)
Western blot confirmation (specifics bands between 24 and 35 kDa)	**73 (100%)**
5 bands	60 (82.2%)
4 bands	7 (9.6%)
3 bands	3 (4.1%)
Asymptomatic	**23 (31.5%)**
EOSINOPHIL RELATED ORGAN INVOLVEMENT	
Skin	**29 (33.7%)**
Skin rash	18 (24.7%)
Urticaria	7 (9.6%)
Angioedema	5 (6.8%)
Digestive	**11 (15.1%)**
Diarrhoea	6 (8.2%)
Abdominal pain	3 (4.1%)
Biopsy-proven colitis*	1 (1.4%)
Icterus	1 (1.4%)
Mesenteric panniculitis	1 (1.4%)
Respiratory	**13 (17.8%)**
Dyspnoea and/or cough	7 (9.6%)
Bilateral pulmonary infiltrates†	4 (5.4%)
Bronchospasm	2 (2.7%)
Vascular	**5 (6.8%)**
Venous thrombosis	5 (6.8%)
Arterial thrombosis	1 (1.4%)
Cardiac	**1 (1.4%)**
Endomyocardial fibrosis	1 (1.4%)
PARASITE RELATED MANIFESTATIONS	
Uveitis	2 (2.7%)
Liver abscess	3 (4.1%)
OTHER SYMPTOMS	
Muscular involvement	**2 (2.7%)**
Myalgia	1 (1.4%)
CK elevation	1 (1.4%)
Necrosing myositis	1 (1.4%)
Constitutional symptoms	**5 (6.8%)**
Fever	2 (2.7%)
Weight loss	3 (4.1%)

AEC: absolute eosinophil count ;CRP: C reactive protein; † Computed tomography scan finding; * With eosinophilic infiltrate.

Table 7. Schistosomiasis: Demographic, clinical, and biological features

	N = 25
Age at diagnosis, median (range), years	**25.5 (6.5-70.9)**
Adults	19 (76%)
Under 18 years old	6 (24%)
Male	**22 (88%)**
Allergic disorders	**1 (4%)**
Stay in Africa	**25 (100%)**
Antiparasitic treatment	
Praziquantel	22 (88%)
Ivermectin	8 (32%)
Albendazole	5 (20%)
Antiparasitic treatment duration, median (range), days	**2 (1-14)**
Glucocorticoids use	**0**
AEC, median (IQR), x 10^9/L	**1.1 (0.8-3.0)**
Eosinophilia (0.5-1.5 x 10^9/L)	16 (64%)
Hypereosinophilia (>1.5 x 10^9/L)	9 (36%)
CRP, median (IQR), mg/L	**1.5 (1.5-8)**
CRP > 5 mg/l	9 (32%)
Western blot confirmation	**22 (88%)**
Parasitic direct identification	**14 (56%)**
Stool	8 (32%)
Urine	6 (24%)
Asymptomatic	**2 (8%)**
EOSINOPHIL RELATED ORGAN INVOLVEMENT	
Skin	**2 (8%)**
Skin rash	1 (4%)
Urticaria	1 (4%)
Angioedema	1 (4%)
Digestive	**11 (44%)**
Diarrhoea	8 (32%)
Abdominal pain	3 (12%)
Biopsy-proven colitis*	1 (4%)
Chylous ascites	1 (4%)
Respiratory	**1 (4%)**
Dyspnoea and/or cough	1 (4%)
Vascular	**1 (4%)**
Venous thrombosis	1 (4%)
PARASITE RELATED MANIFESTATIONS	
Haematuria	8 (32%)
Bladder calcifications	2 (8%)
Liver abscess	1 (4%)
Occipital pseudotumor£	1 (4%)
OTHER SYMPTOMS	
Constitutional symptoms	**3 (12%)**
Fever	2 (8%)
Weight loss	1 (4%)

AEC: absolute eosinophil count ; CRP: C reactive protein;
* With eosinophilic infiltrate; £ With pathological evidence of the parasite.

Table 8. Filariasis: Demographic, clinical, and biological features

	N = 10
Age at diagnosis, median (range), years	36.1 (1.7-68
Adults	8 (80%)
Under 18 years old	2 (20%)
Male	4 (40%)
Allergic disorders	3 (30%)
Stay in endemic area	10 (100%)
Central et western Africa	8 (80%)
French Guyana	1 (10%)
South America	1 (10%)
Antiparasitic treatment	
Ivermectin	9 (90%)
Albendazole	6 (60%)
Flubendazole	1 (10%)
Praziquantel	3 (30%)
Diethylcarbamazine	2 (20%)
Antiparasitic treatment duration, median (range), days	15 (2-28)
Glucocorticoids use	1 (10%)
AEC, median (IQR), x 10^9/L	1.8 (1.2-3.0)
Eosinophilia (0.5-1.5 x 10^9/L)	4 (40%)
Hypereosinophilia (>1.5 x 10^9/L)	6 (60%)
CRP, median (IQR), mg/L	6 (1.5-8.0)
CRP > 5 mg/l	4 (40%)
Positive immunoelectrophoresis	3 (30%)
Asymptomatic	0
EOSINOPHIL RELATED ORGAN INVOLVEMENT	
Skin	7 (70%)
Urticaria	2 (20%)
Angioedema ‡	5 (50%)
Respiratory involvement	2 (20%)
Bilateral pulmonary infiltrates†	1 (10%)
Bronchospasm	1 (10%)
PARASITE RELATED MANIFESTATIONS	
Ocular *larva migrans*	4 (40%)
Cutaneous *larva migrans*	1 (10%)
OTHER SYMPTOMS	
Myalgia	1 (10%)

AEC: absolute eosinophil count ; CRP: C reactive protein; † Computed tomography scan finding; ‡ Corresponding to Calabar swelling for some authors.

Table 9. Fasciolasis: Demographic, clinical, and biological features

	N = 9
Age at diagnosis, median (range), years	63.7 (9.4-88.7)
Adults	8 (89%)
Under 18 years old	1 (11.%)
Male	3 (33%)
Watercress consumption	3 (33%)
Allergic disorders	3 (33%)
Antiparasitic treatment	
Albendazole	3 (33%)
Triclabendazole	2 (22%)
Unspecified	4 (44%)
Antiparasitic treatment duration, median (range), days	5 (1-15)
Glucocorticoids use	0
AEC, median (IQR), x 10^9/L	3.0 (2.0-4.0)
Eosinophilia (0.5-1.5 x 10^9/L)	0
Hypereosinophilia (>1.5 x 10^9/L)	9 (100%)
CRP, median (IQR), mg/L	20 (17-65)
CRP > 5 mg/l	7 (78%)
Positive *Fasciola hepatica* immunoelectrophoresis	2 (22%)
EOSINOPHIL RELATED ORGAN INVOLVEMENT	
Skin	4 (44%)
Skin rash	3 (33%)
Urticaria	1 (11%)
Digestive	5 (56%)
Abdominal pain	4 (44%)
Diarrhoea	1 (11%)
Respiratory involvement	1 (11%)
Eosinophilic pleural effusion	1 (11%)
PARASITE RELATED MANIFESTATIONS	
Liver abscess	1 (11%)
OTHER SYMPTOMS	
Fever	1 (11%)

AEC: absolute eosinophil count ; CRP: C reactive protein.

Table 10. Strongyloidiasis: Demographic, clinical, and biological features

	N = 8
Age at diagnosis, median (range), years	**39.1 (4.5-64.4)**
Adults	7 (87.5%)
Under 18 years old	1 (12.5%)
Male	**5 (62.5%)**
Allergic disorders	**1 (12.5%)**
Stay in endemic area	**8 (100%)**
North Africa	3 (37.5%)
Central America	2 (25.0%)
South-East Asia	1 (12.5%)
Portugal	1 (12.5%)
France overseas	1 (12.5%)
Antiparasitic treatment	
Ivermectin	8 (100%)
Albendazole	2 (25.0%)
Flubendazole	1 (12.5%)
Praziquantel	2 (25%)
Antiparasitic treatment duration, median (range), days	**2 (1-15)**
Glucocorticoids use	**3 (37.5%)**
AEC, median (IQR), x 10^9/L	**2.0 (1.6-3.3)**
Eosinophilia (0.5-1.5 x 10^9/L)	2 (25.0%)
Hypereosinophilia (>1.5 x 10^9/L)	6 (75.0%)
CRP, median (IQR), mg/L	**17 (10-55)**
CRP > 5 mg/l	5 (62.5%)
Asymptomatic	**2 (25.0%)**
EOSINOPHIL RELATED ORGAN INVOLVEMENT	
Cutaneous involvement	**2 (25%)**
Skin rash	1 (12.5%)
Urticaria	1 (12.5%)
Gastro-intestinal involvement	**2 (25.0%)**
Diarrhoea	1 (12.5%)
Jejunitis†	1 (12.5%)
Respiratory involvement	**3 (37.5%)**
Dyspnoea and/or cough	1 (12.5%)
Bilateral pulmonary infiltrates†	2 (37.5%)
PARASITE RELATED MANIFESTATIONS	
Cutaneous *larva migrans*	1 (12.5%)
OTHER SYMPTOMS	
Fever	1 (12.5%)

AEC: absolute eosinophil count ; CRP: C reactive protein;

† Computed tomography scan finding;

Table 11. Trichinosis: Demographic, clinical, and biological features

	N = 5
Age at diagnosis, median (range), years	63.8 (44.6-78.2)
Adults	5 (100%)
Male	3 (60%)
Allergic disorders	3 (60%)
Antiparasitic treatment	
Albendazole	4 (80%)
Ivermectin	4 (80%)
Praziquantel	2 (40%)
Antiparasitic treatment duration, median (range), days	15 (2-15)
Glucocorticoids use	1 (20%)
AEC, median (IQR), x 10^9/L	1.7 (1.3-8.0)
Eosinophilia (0.5-1.5 x 10^9/L)	2 (40%)
Hypereosinophilia (>1.5 x 10^9/L)	3 (60%)
CRP, median (IQR), mg/L	6 (6-13)
CRP > 5 mg/l	4 (80%)
Western blot confirmation	2 (40%)
Asymptomatic	0
EOSINOPHIL RELATED ORGAN INVOLVEMENT	
Skin	2 (40%)
Urticaria	1 (20%)
Face oedema	1 (20%)
Digestive	2 (40%)
Diarrhoea	2 (40%)
Respiratory	2 (40%)
Dyspnoea and/or cough	1 (20%)
Bronchospasm	1 (20%)
Vascular	1 (20%)
Venous thrombosis	1 (20%)
Cardiac	1 (20%)
Myopericarditis	1 (20%)
OTHER SYMPTOMS	
Myalgia	3 (60%)
CK elevation	2 (40%)

AEC: absolute eosinophil count; CRP: C reactive protein.

Table 12. Toxocariasis clinical manifestations according to AEC level (x 10^9/L)

	AEC <0.5 (N=38)	0.5 <AEC <1.5 (N=40)	AEC >1.5 (N=33)
Asymptomatic	**13 (34.2%)**	**18 (45%)**	**5 (15.1%)**
EOSINOPHIL RELATED ORGAN INVOLVEMENT			
Skin	**21 (55.3%)**	**17 (42.5%)**	**12 (36.4%)**
Skin rash	1 (2.6%)	9 (22.5%)	9 (27.3%)
Urticaria	13 (34.2%)	5 (12.5%)	2 (6.1%)
Angioedema	8 (21.1%)	5 (12.5%)	-
Digestive	**-**	**4 (10%)**	**7 (21.2%)**
Diarrhoea	-	2 (5%)	4 (12.1%)
Abdominal pain	-	1 (2.5%)	2 (6.1%)
Biopsy-proven colitis*	-	1 (2.5%)	-
Icterus	-	1 (2.5%)	-
Mesenteric panniculitis	-	-	1 (3.0%)
Respiratory	**1 (2.6%)**	**4 (10%)**	**9 (27.3%)**
Dyspnoea and/or cough	1(2.6%)	3 (7.5%)	4 (12.1%)
Bilateral pulmonary infiltrates†	-	-	4 (12.1%)
Bronchospasm	-	1 (2.5%)	1 (3.0%)
Vascular	-	-	**5 (15.2%)**
Venous thrombosis	-	-	5 (15.2%)
Arterial thrombosis	-	-	1 (3.0%)
Cardiac	**-**	**-**	**1 (3.0%)**
Endomyocardial fibrosis	-	-	1 (3.0%)
PARASITE RELATED MANIFESTATIONS			
Uveitis	3 (7.9%)	1 (2.5%)	1 (3.0%)
Liver abscess	-	-	3 (9.1%)
OTHER SYMPTOMS			
Muscular involvement	-	**2 (5%)**	-
Myalgia	-	1 (2.5%)	-
CK elevation	-	1 (2.5%)	-
Necrosing myositis	-	1 (2.5%)	-
Constitutional symptoms	**-**	**2 (5%)**	**3 (9.1%)**
Fever	-	1 (2.5%)	1 (3.0%)
Weight loss	-	1 (2.5%)	2 (6.1%)

AEC: absolute eosinophil count ;CRP: C reactive protein; † Computed tomography scan finding;
* With eosinophilic infiltrate.

AUTEUR : MIDOL Charles

Date de soutenance : 24 novembre 2021

Titre de la thèse : Manifestations cliniques des éosinophilies d'origine parasitaire

Thèse - Médecine - Lille « 2021 »
Cadre de classement : *Médecine interne*
DES + spécialité : *Médecine interne*

Mots-clés : parasites, helminthes, éosinophile, hyperéosinophilie, syndrome hyper-éosinophilique, toxocarose, bilharziose, filariose, distomatose, anguillulose, trichinose.

Résumé :

Objectifs : Les helminthiases sont une cause fréquente d'éosinophilie avec un large spectre de manifestations cliniques. Le but de notre étude était de décrire les symptômes associés aux helminthiases chez des patients consultant dans un CHU de France métropolitaine, et de les analyser en fonction du parasite en cause et du taux d'éosinophiles sanguins.

Méthodes : Dans cette étude rétrospective monocentrique, les patients étaient inclus en cas d'helminthiase diagnostiquée, avec une éosinophilie (EO) > 0.5 x 10^9/L. Ils étaient identifiés grâce à la base de données du laboratoire de parasitologie du CHU de Lille entre 2010 et 2020. En l'absence d'autre explication à l'éosinophilie, le diagnostic d'helminthiase était retenu en cas de positivité d'un test sérologique, et avec (i) un test de confirmation antigénique, et/ou (ii) en cas de critères cliniques évocateurs, et (iii) lorsque le suivi du patient concluait à l'efficacité du traitement antiparasitaire. Pour discuter la répartition des manifestations cliniques, un groupe comparateur de patients atteints de SHE idiopathiques était constitué à partir de la cohorte nationale du CEREO.

Résultats : 131 patients (dont 34% de femmes) ont été inclus, d'âge médian [2 ;91] de 51 ans. Les cas de toxocaroses étaient les plus fréquents (n=73), suivi des bilharzioses (n=25), filarioses (n=10), distomatoses (n=9), anguilluloses (n=8), trichinoses (n=5) et un cas d'anisakiase. Dans la toxocarose les manifestations étaient cutanées (34% des cas), respiratoires (18%), gastro-intestinales (15%) vasculaires (7%) avec essentiellement des manifestations thrombo-emboliques (7% de thromboses veineuses, 1 cas de thrombose artérielle) et cardiaque (1%). La comparaison entre les helminthiases symptomatiques avec hyperéosinophilie (N=52) et la cohorte de SHE idiopathiques du CEREO (N=148) montre une répartition comparable des atteintes cutanées, gastro-intestinales, respiratoires, vasculaires et oculaires ou cérébrales. Le taux d'éosinophiles était significativement plus élevé chez les patients symptomatiques par rapport aux asymptomatiques (médiane 1.7 [IQR 1.0-4.0] contre 1.2 [IQR 1.1-1.7] x 10^9/L ; p=0.037).

Conclusion : Au-delà des manifestations évocatrices de certaines parasitoses, les manifestations cliniques liés à l'éosinophilie sont comparables aux atteintes des SHE idiopathiques, et plus fréquentes en cas d'HE que d'EO, soulignant le rôle central des éosinophiles dans la survenue des manifestations d'organes.

<u>Composition du Jury</u> :

Président : Professeur Éric HACHULLA
Assesseurs : Professeur Boualem SENDID
Docteur Fanny VUOTTO
Directeur de thèse : Docteur Guillaume LEFEVRE