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Distal ischemia as the initial presentation of hypereosinophilic syndrome-related arterial involvement: A case study and literature review

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1. Introduction

Blood eosinophilia may occur in primary systemic vasculitides (*e.g.* polyarteritis nodosa (PAN), eosinophilic granulomatosis with polyangiitis (EGPA) [1,2], but some medium- and/or small-sized vessel manifestations may be associated with blood eosinophilia, without fulfilling criteria for primary systemic vasculitides [3,4]. In 2011, the International Working Group on Eosinophil Disorders (ICOG-EO) suggested that patients with symptoms related to medium- and/or small-sized vessel involvement (including unexplained thrombosis and/or stenosis) associated with blood eosinophilia > 1.5 G/L fulfill criteria for HES [5]. Venous thrombotic complications have been reported during the course of HES, affecting up to 25% of patients [6,7] contrasting with limited data regarding arterial involvement [8]. Hence, we aimed to describe medium- and small-sized arteries involvement associated to blood eosinophilia in the absence of defined systemic vasculitis. Particularly, we present here patients with distal ischemia and blood eosinophilia, and perform a review of the literature summarizing presentation, management, and outcome of this rare condition.

We conducted a multicenter retrospective study using the French Vasculitis Study Group (FVSG) network. Inclusion criteria were the presence of blood eosinophilia > 1.0 G/L and arterial involvement defined as digital ischemia, arterial thrombosis and/or arterial abnormalities on vascular imaging. Patients fulfilling criteria for both primary and secondary systemic vasculitis were excluded [3,4] as were patients with cardiac embolism and thrombophilia. Clinical, biological and radiological data for both eosinophilia and vasculitis were collected. We systematically reviewed the literature for reports of patients presenting with arterial involvement and eosinophilia, with a focus on patients presenting with distal ischemia.

2. Patients' characteristics and diagnostic workups

Thirteen patients (12 male, 1 female) from 8 centers were included. Table 1 summarizes the clinical manifestations of both our patients and those previously reported in the literature. Median age at disease onset was 43 (28–61.2) years and arterial vascular involvement involved most frequently upper limbs (92%) Extravascular manifestation were rare and included mostly constitutional symptoms (30%) and arthralgia (15%). Both Anti-Neutrophil Cytoplasmic Antibody (ANCA) and cryoglobulin were negative in all tested patients. Blood eosinophilia was diagnosed before arterial vascular involvement in 7 cases and concomitantly in 6. Lymphocyte immunophenotyping was unremarkable in all patients, and so was the search for FIP1L1-PDGFRA fusion gene transcript. Overall, all patients could be classified as having idiopathic hypereosinophilic syndrome (HES_I). Doppler US, performed in 12 patients, showed abnormal findings in 10 cases (78%), *i.e.* thrombosis, stenosis with arterial occlusion ($n = 4$ each), and both in 2 cases. Fig. 1 illustrates arterial occlusion in one patient who had angiography.

3. Therapeutic management and response to treatment

First-line therapy included GCs in 10 (77%) cases associated with cyclophosphamide and hydroxycarbamide in one case each. Symptomatic treatments included antiplatelet agents ($n = 12$, 92%), anticoagulant therapy ($n = 9$, 69%), calcium channel blockers ($n = 5$, 38%) and iloprost ($n = 4$, 30%). Patients' outcomes after first line therapy are shown in Table 1. Besides symptomatic treatments, 9 Patients required further line treatments, consisting of anti-eosinophil drugs in all cases among which 4 patients received concomittant immunsuppressant therapy. Altogether, the most frequent anti-eosinophil drug was interferon-alpha ($n = 6$, 50%), cyclosporine ($n = 3$, 25%), hydroxycarbamide ($n = 2$, 17%) and imatinib mesylate (n = 2, 17%). Among the 12 patients with follow-up, the last treatment resulting in sustained remission was GCs in 4 cases, immunosuppressive agents in 2 cases and eosinophil-targeting drug in 6 cases. Finally, despite initial severity, all patients who achieved eosinophil count normalization showed concomitant clinical remission (yet including a patient that required trans metatarsal amputation prior to remission). Last, a patient treated with antiplatelets, heparin and iloprost but without GCs nor anti-eosinophil drugs underwent amputation of the 4th finger of the right hand, before being lost to follow-up after surgery.

4. Review of the literature

The literature search identified 20 additional cases from 18 different

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Table 1
Patients' characteristics from our personal series and from the literature review.

	Present series		Literature review		Both	
Demography	*n* = 13	%	*n* = 20	%	*n* = 33	%
Median age (year)	43	(28–61,2)	36,5	(31–56,3)	38	(29–58,7)
Male	12	92%	15	75%	27	82%
Vascular involvement						
Upper Limb	12	92%	14	70%	26	79%
Lower Limb	9	69%	12	60%	21	64%
Both	8	62%	6	30%	14	42%
Pulse abolition	7	54%	14	70%	21	64%
Digital ischemia	11	85%	17	85%	28	85%
Acrocyanosis	7	54%	15	75%	22	66%
Paresthesia	4	30%	6	30%	10	30%
Cutaneous involvement	11	85%	18	90%	29	88%
Necrosis	10	77%	12	60%	22	66%
Ulcers	9	70%	9	45%	18	55%
Purpura	3	23%	2	10%	5	15%
Splinter Hemorrhages	6	46%	2	10%	8	24%
Other involvement						
Constitutional symptoms	4	30%	4	20%	8	24%
Arthralgia	2	15%	0	0%	2	6%
Neurological	1	7%	3	15%	4	12%
Cardiac	1	7%	2	10%	3	9%
Respiratory	1	7%	0	0%	1	3%
Muscular, ENT, Ocular, Renal	0	0%	0	0%	0	0%
Complications						
Amputation	2	15%	6	30%	8	24%
Angioplasty	0	0%	3	15%	3	9%
Evolution after first-line therapy						
Remission	9	75%	13	72%	22	73%
Need for Steroids sparing drug	2	17%	0	0%	2	7%
Refractory Disease	3	25%	5	28%	8	27%
Relapse	3	25%	6	33%	9	30%
Further line therapy	9	70%	–	–	–	–
Immunosuppressive Agent	6	66%	–	–	–	–
Eosinophil-targeting drug	9	100%	–	–	–	–
Number of lines of treatment	2,5	[1–3]	–	–	–	–

articles published between 1995 and 2018 [9–26] with twelve of them originated from Asia. Such patients' clinical characteristics are summarized in Table 1. Two patients were initially considered as having thromboangiitis obliterans (TAO, Buerger's disease) and 7 had Kimura's disease (KD). First-line therapy included symptomatic treatment in all cases and GCs in 17 (85%) with remission in 13 (65%) paitents. All patients with second-line therapy received GCs, in combination with immunosuppressive agents in 4 (33%) and anti-eosinophil drugs in 3 (23%). All patients but one finally achieved complete remission with further-line treatments, but 5 patients required limb amputation and one died.

5. Discussion

Here, we report on a case series of 13 patients presenting with distal ischemia as the initial presentation of medium- and small-sized vessel involvement related to HES. Most patients were middle-aged men with vascular and cutaneous features but few extravascular manifestations. Interestingly, despite severe initial presentation (limb amputation), disease manifestations tended to correlate with blood eosinophilia in all patients, with an overall fair prognosis once blood eosinophil counts normalized. Although vascular involvement depicted herein could mimic those reported during other conditions like PAN or TAO, only four patients were current smokers at baseline with no effect of smoking cessation on disease manifestations, and there was no other manifestation suggestive of PAN.

In the context of chronic blood eosinophilia > 1.5 G/L, the ICOG-EO suggested the presence of thrombosis was a sufficient criteria defining eosinophil-related damage and thus was diagnostic for HES [5]. To avoid delayed diagnosis and onset of disease-specific treatment, it is of paramount importance that vasculitis-treating physicians be aware that HES-related arterial involvement is a diagnosis to consider in patients presenting with limb-threatening disease and eosinophilia.

Despite the low number of patients considered herein, our work provides fresh data regarding the therapeutic management and outcome of this condition. Patients' clinical evolution strongly correlated with eosinophil counts and GCs alone seemed to be highly effective as a first-line therapy with 75% of response and one third of patients achieving sustained remission after the first course of treatment. Although it is impossible to draw definite conclusion from such limited population, our data suggest that, in cases of GC failure or dependency, eosinophil-targeted drugs (*e.g.* interferon-alpha, cyclosporine and hydroxycarbamide) seem to provide the higher rates of sustained remission. This finding could be one of the key message of our work, as eosinophils-targeted drugs may not represent the most “traditionally used” treatments in this situation.

In conclusion, medium- and small-sized vessel involvement is a rare disease manifestation of HES, presenting commonly as distal ischemia. Despite initial severe presentation, GCs are effective, and outcomes were fair once eosinophil blood count normalized. In case of GC failure or dependency, eosinophil-targeted drugs seem to be appealing second-line treatments.

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Conflict of interests

None.

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