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BRIEF REPORT

FIP1L1-PDGFR α -Associated Hypereosinophilic Syndrome as a Treatable Cause of Watershed Infarction

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BACKGROUND AND PURPOSE: Ischemic stroke has been reported in various conditions associated with eosinophilia. *FIP1L1-PDGFR α* fusion ([Fip1-like 1-platelet-derived growth factor receptor alpha]; *F/P*) leads to the proliferation of the eosinophilic lineage and thus to a clonal hypereosinophilic syndrome that is highly responsive to imatinib.

METHODS: We previously reported on a nationwide retrospective study of 151 patients with *F/P*-associated clonal hypereosinophilic syndrome. Patients from this cohort with a clinical history of ischemic stroke (as well as 2 additional cases) were further analyzed to better define their clinical picture and outcomes.

RESULTS: Sixteen male patients (median age, 51 [43–59] years) with low-to-intermediate cardiovascular risk were included. Median National Institutes of Health Stroke Scale was 4 (range, 1–6). Most cerebral imaging disclosed multiple bilateral infarctions of watershed distribution (69%). Despite frequent cardiac involvement (50%), cardiac thrombus was evidenced in a single patient and, according to the TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment), 62.5% of strokes were presumably of undetermined etiology. Among the 15 patients treated with imatinib, and after a median follow-up of 4.5 years, stroke recurred in only 3 patients (consisting of either cardio embolic or hemorrhagic events, unrelated to the first episode).

CONCLUSIONS: *F/P*+ clonal hypereosinophilic syndrome is a diagnosis to consider in patients with unexplained ischemic stroke and hypereosinophilia (especially in the setting of multiple cortical borderzone distribution) and warrants prompt initiation of imatinib.

GRAPHIC ABSTRACT: An online [graphic abstract](#) is available for this article.

Key Words: eosinophils ■ imatinib mesylate ■ leukemia ■ stroke

Hypereosinophilic syndrome (HES) is a protean condition defined by chronic blood eosinophilia ≥ 1.5 G/L (≥ 1 month) and eosinophil-related organ damage. *FIP1L1-PDGFR α* ([Fip1-like 1-platelet-derived growth factor receptor alpha]; *F/P*) fusion results in a constitutively active tyrosine kinase which induces uncontrolled cell proliferation and can lead to various hematologic malignancies, including acute leukemia and far more frequently

F/P+ myeloid neoplasm with eosinophilia (*F/P*+ MN-eo, formerly chronic eosinophilic leukemia).¹ Accounting for $\approx 10\%$ of all patients with HES, *F/P*+ MN-eo is the main cause of clonal HES and is highly responsive to imatinib.²

Ischemic strokes have previously been reported in various conditions associated with eosinophilia, including clonal or reactive HES.³ Although eosinophilic cardiomyopathy is often suspected to be the trigger for stroke,

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the potential role of direct eosinophil-related toxicity is increasingly suspected.⁴ To date, only a few cases of ischemic strokes occurring in the setting of *F/P+* MN-eo have been reported.⁵

Here, we aim to focus on the clinical characteristics, imaging findings and outcomes of patients with ischemic stroke and molecularly defined *F/P+* clonal HES.

METHODS

We recently conducted a comprehensive retrospective study of all patients with a positive search for *F/P* fusion in France between 2003 and July 2019.⁶ Among the 195 patients identified, 151 with *F/P+* MN-eo and available clinical data were included. Among the latter, we further reviewed the medical files and imaging features of patients with a clinical history of ischemic stroke. Strokes' subtypes were categorized according to the TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment)⁷ and depending on the presence or absence of possible or probable cardioembolic eosinophilic cardiomyopathy. This study was conducted in compliance with the Helsinki declaration (as revised in 2008), the MR004 French legislation, was approved by Foch Hospital's ethical review board 2 (IRB00012437, approval number No. 20-07-07) and was registered at the Institut National des Données de Santé. All patients received oral and written information regarding the study and did not object to the processing of their personal data. The authors declare that all supporting data are available within the article and in the [Data Supplement](#). Full details of the methods section are available in the [Data Supplement](#).

RESULTS

Among the 151 previously reported patients with *F/P+* MN-eo, 14 (9.3%) had at least one ischemic stroke. As 2 additional patients with *F/P+* MN-eo and stroke were diagnosed since 2019, 16 male patients were finally included. General characteristics, stroke clinical presentation and imaging findings, cardiovascular risk, and stroke cause are listed in the Table. Of note, none were under imatinib therapy at the time of stroke. Besides a higher rate of cardiac involvement (50% versus 15%, $P=0.0039$), patients' clinical and laboratory findings (summarized in Table I in the [Data Supplement](#)) did not differ between *F/P+* MN-eo patients with or without stroke. Stroke was the initial disease manifestation of *F/P+* MN-eo in 13 (81%) patients. Eleven (69%) patients displayed stroke with a border zone distribution (Figure) among which a single patient had a history of severe hypotension (case No. 2). Gadolinium injection was performed in 11 (69%) patients, among which 8 (73%) showed white matter lesion enhancement attributed to blood-brain barrier disruption.

The detailed etiological workup for each patient is provided in Table II in the [Data Supplement](#). All patients had a transthoracic echocardiogram, along with a transesophageal echocardiogram in 5 (31%) cases and a

cardiac MRI in 9 (56%) cases. Eight (50%) patients were diagnosed with specific HES-related cardiac involvement, consisting of endomyocardial fibrosis ($n=2$) or myocarditis ($n=6$), among which a single patient showed evidence of left ventricular thrombus (case No. 16). Highly sensitive troponin levels were increased in 7 of 11 tested patients (63%; median 430 [13–1414] pg/mL) including all patients with cardiac involvement and available data.

All patients received either antiplatelets ($n=10$, 62.5%), anticoagulants ($n=6$, 37.5%), or intravenous thrombolysis ($n=1$, case No. 13). None of the 8 (50%) patients initially treated with steroids normalized their Absolute Eosinophilic Count (AEC). Subsequently, all patients but one (case No. 5, who received steroids and chemotherapy) were successfully treated with imatinib (with both normalization of AEC and negative testing for *F/P* fusion transcript within one month). After a median follow-up of 4.5 [1–11] years, stroke recurred in 3 patients with normal AEC while on treatment with imatinib, consisting of 2 focal cardioembolic ischemic strokes (in a context of atrial fibrillation and cardiac thrombus due to persistent apical akinesis: case No. 1 and 3, respectively) and one hemorrhagic stroke (in a patient under treatment with anticoagulants for atrial fibrillation: case No. 4).

DISCUSSION

Strokes in the setting of eosinophilia are generally considered of cardioembolic origin, attributed to mural thrombi secondary to endomyocardial fibrosis. In this line, in the largest series of patients with *F/P+* MN-Eo, patients with stroke indeed had more frequent eosinophil-related cardiac disease than those without.⁶ Additionally, some authors suggested that strokes in this setting could be related to micro embolism (as evidenced by high intensity transient signals on a patient's transcranial Doppler)⁸ or by the hypoperfusion of cerebral small vessels, resulting in a lower washout or clearance of emboli.⁹ Conversely, some patients reported herein lacked evidence of cardiac involvement (despite comprehensive investigations) and left ventricular thrombus was evidenced in a single patient. Likewise, if cardioembolic stroke often present as multiple bilateral lesions, watershed distribution is not frequently associated with this condition, accounting for <10% of cases in a large series of strokes with such distribution.¹⁰ Hence, given the previous reports of cardiovascular involvement in HES¹¹ and the widespread procoagulant effects of eosinophils,⁴ one might also speculate that border zone infarcts rather reflect broad eosinophil-related endothelial toxicity. In this line, watershed infarctions displayed herein are strikingly similar to those reported within the full-spectrum of other eosinophil-associated diseases including reactive,¹² lymphocytic,¹³ idiopathic variants of HES³ and Eosinophilic Granulomatosis with Polyangiitis.¹⁴ Moreover, abundant intravascular eosinophils or eosinophilic

Table. Clinical, Brain Imaging Findings, and Cardiac Evaluation of F/P+ MN-eo Patients With Stroke

Patient	Age, y	CV risk*	Clinical presentation	NIHSS	AEC, (×10 ⁹ /L)	Brain imaging findings	Stroke cause according to TOAST classification	Cardioembolic eosinophilic cardiomyopathy†	Rankin at M3	Recurrence of stroke (time to recurrence)
Case 1	66	High (7%)	Right brachio-facial paresis, hypoesthesia, aphasia	5	28.5	CT: multiple lacunar strokes	Small-vessel disease: lacune	Possible	0	Yes IS (10 y)
Case 2	58	Moderate (2%)	Coma (context of pulmonary sepsis)	NA	13	MRI: bilateral watershed infarctions	Other determined cause: low-flow over septic shock	Possible	6	No
Case 3‡	26	Low (0%)	Left hemiparesis, fever	3	20	MRI: bilateral watershed infarctions	Possible cardioembolic stroke: hypokinetic LV segment	Probable	3	Yes IS (4 y)
Case 4	67	Moderate (4%)	Left hemiparesis	3	9.9	MRI: bilateral watershed infarctions	Undetermined	No	1	Yes HS (6 y)
Case 5	49	Moderate (1%)	Dysarthria, aphasia, right hypoesthesia	4	3.4	MRI: deep left middle cerebral artery territory	Undetermined	No	1	No
Case 6	57	Very high (MI)	Aphasia	4	2.8	MRI: bilateral watershed infarctions	Possible cardioembolic stroke: MI < 6 mo	No	3	No
Case 7	51	Moderate (1%)	Right hemiparesis, ataxia	4	11	MRI: bilateral watershed infarctions	Undetermined	No	2	No
Case 8	43	Low (0%)	Cerebellar syndrome, left hollow hand, fever	2	6	MRI: bilateral watershed infarctions	Undetermined‡	Possible	2	No
Case 9	42	Very high (diabetes, MI)	Dizziness, ataxia	1	6.5	MRI: bilateral watershed infarctions	Cardioembolic stroke: akinetic LV segment	No	0	No
Case 10	51	Moderate (3%)	Cerebellar syndrome, right hemiparesis, hypoesthesia	6	36	MRI: bilateral watershed infarctions	Undetermined	No	2	No
Case 11	61	Very high (diabetes)	Dizziness, binocular diplopia, vomiting, ataxia	1	3	CT: multiple right hemispheric infarctions	Undetermined	No	1	No
Case 12	39	Low (0%)	Balance disorder, hypoesthesia, hemiparesis, fever	2	4	MRI: bilateral watershed infarctions	Undetermined§	Possible	1	No
Case 13	63	Moderate (2%)	Right hemiparesis, hypoesthesia	6	1.9	MRI: left anterior choroidal artery infarctions	Undetermined	No	1	No
Case 14	32	Low (0%)	Left hemiparesis	3	9.4	MRI: bilateral punctiform multiple infarctions	Undetermined‡	Possible	2	No
Case 15	51	Moderate (2%)	Left hemiparesis, hypoesthesia	5	17	MRI: bilateral watershed infarctions	Undetermined‡	Possible	3	No
Case 16	54	Moderate (1%)	General psychomotor slowing	3	21	MRI: bilateral watershed infarctions	Cardioembolic stroke: LV thrombus	Probable	1	No

AEC indicates absolute eosinophil counts; CT, CT-scan; CV, cardiovascular; F/P+ MN-eo, *FIP1L1-PDGFRα*-positive myeloid neoplasm with eosinophilia; HS, hemorrhagic stroke; IS, ischemic stroke; LV, left ventricle; M3, after 3 mo; MI, myocardial infarction; MRI, magnetic resonance imaging; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Cardiovascular risk was calculated according to the 2016 European Guidelines (SCORE result is indicated if applicable).

†As defined in Methods in the [Data Supplement](#).

‡Case previously reported.⁵

§Endomyocardial fibrosis and myocarditis are not considered as potential causes of cardioembolic stroke in the TOAST classification (1993).⁷

vasculitis have previously been reported in a few pathology reports from cerebral biopsies of similar patients.¹² Yet, the sparing of lacunar regions is not consistent with

small-vessel toxicity. Hence, one could hypothesize that the pathophysiological process underpinning such watershed strokes could rather be multifactorial, involving both

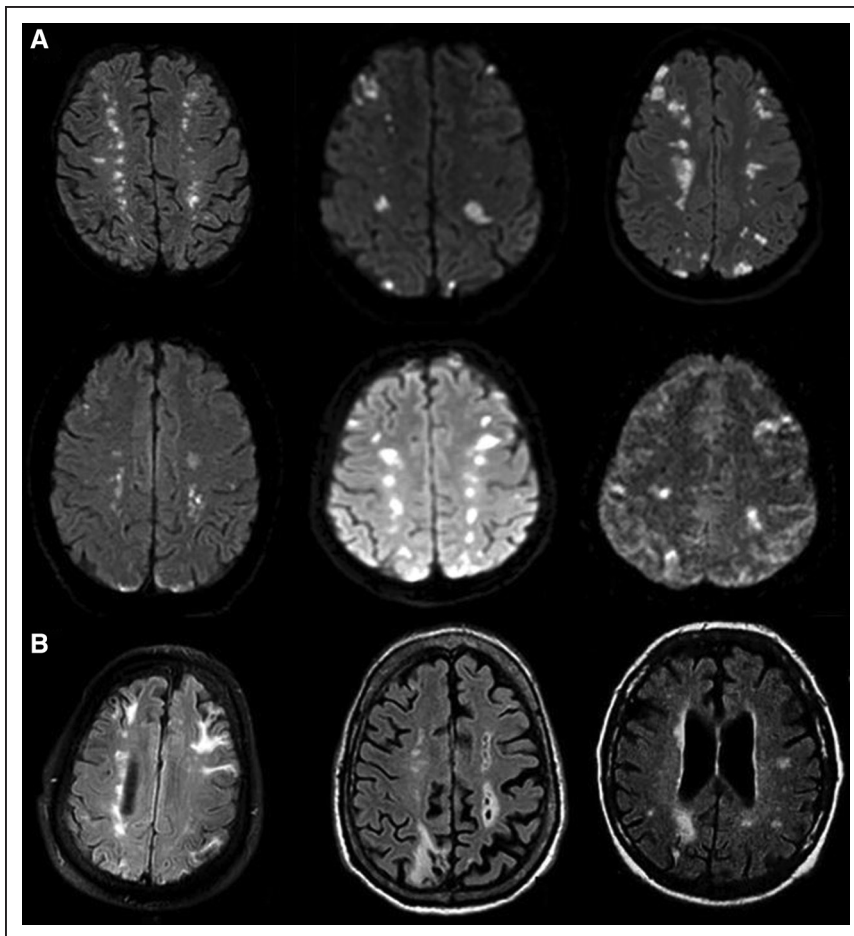


Figure. Magnetic resonance imaging (MRI) findings in patients with stroke related to FIP1L1-PDGFR α -positive myeloid neoplasm with eosinophilia (F/P+ MN-eo) mostly disclosed cortical border zone infarcts.

Brain MRI of 9 different patients with F/P+ MN-eo disclosing multiple acute or subacute strokes with watershed distribution. **A**, Diffusion-weighted MRIs (from left to bottom: patients No. 2, 3, 12, 16, 10). **B**, T2-FLAIR MRIs (from patients No. 15, 7, and 4).

(micro) cardioembolism (as illustrated by the high rates of cardiac involvement reported) and eosinophil-related endothelial toxicity.

From a therapeutic viewpoint, these results suggest that, in patients with F/P+ MN-eo and stroke, normalizing AEC on the long run with imatinib could be associated with a low rate of stroke relapse. These findings are in line with previously reported outcomes of 148 F/P+ MN-eo patients, where only 2 (1.3%) patients underwent a clinical relapse while under treatment with imatinib.⁶ Likewise, in other subtypes of HES (including lymphocytic variant¹³) and as demonstrated in a recently published randomized controlled trial evaluating mepolizumab (a monoclonal antibody targeting interleukine-5, a key cytokine involved in eosinophil proliferation and survival) in 108 patients with F/P-negative HES,¹⁵ the occurrence of a new eosinophil-related clinical manifestation while normal AEC is highly unusual. Overall, these findings advocate for prompt initiation of therapy when the diagnosis of HES is ascertained. Last, the pathophysiological process involved herein raises the issue whether anticoagulants (rather than antiplatelets) could be beneficial at the acute phase of stroke.

In conclusion, we report on the first case series of ischemic strokes in the context of molecularly defined clonal hypereosinophilia, affecting up to 10% of patients

with F/P+ MN-eo. Strikingly, most cerebral imaging disclosed bilateral and multiple infarctions with watershed distribution in patients with low-to-moderate cardiovascular risk factors and unsystematic specific cardiac involvement. Prompt initiation of imatinib could prevent the recurrence of stroke and the advent of extra-neurological eosinophil-related symptoms.

ARTICLE INFORMATION

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Supplemental Materials

Online Tables I and II
Expanded Methods

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