Severe asthma with blood hypereosinophilia associated with *JAK2* V617F mutation: a case series

To the Editor:

In a large subset of patients with asthma, blood eosinophilia is common, as a marker of T-helper type 2 cell (Th2) inflammation. Hypereosinophilia (HE), defined by blood eosinophil count >1500 per mm^3, is rare, observed in 0.3% of asthmatic patients [1]. Classically, in the context of uncontrolled asthma and HE, allergic bronchopulmonary aspergillosis, vasculitis or parasitic infection must be investigated [2]. Asthma is also a feature of HE related to various haematological disorders, although respiratory manifestations are rarely isolated in this setting [2].

Between 2009 and 2018, among 1200 patients evaluated in our reference centre for severe asthma in Bichat Hospital, 34 (3%) had blood eosinophil count >1500 per mm^3 on at least two tests. All patients with recurrent HE were asked to undergo a diagnostic work-up including vitamin B12 and tryptase dosage, blood smear examination and screening for the fusion genes FIPL1-PDGFRA (FIP1-like 1–platelet-derived growth factor receptor-α) and ETV6-PDGFRB (ETS variant 6–platelet-derived growth factor receptor-β), Janus kinase 2 (*JAK2*) point mutation, and blood T-cell clone [3, 4]. Bone-marrow analysis was performed when features of lympho- or myeloproliferative disorders were found.

We identified three patients (two females), aged 38 to 65 years, with a *JAK2* (V617F) mutation, approximately 9% of the 34 patients with severe asthma and HE. One patient also had a T-cell clone (patient 2). All had early-onset atopic asthma, with loss of control during adulthood (table 1). HE appeared at age 17, 45 and 55 years, with maximum blood eosinophil count 5540, 4510 and 2000 per mm^3, respectively. For all, previous chest computed tomography imaging had revealed transient pulmonary infiltrates, with evidence of eosinophilic alveolitis on bronchoalveolar lavage in two patients. Two patients had a history of venous or arterial thrombosis requiring long-term anticoagulation. A systematic search for vasculitis or aspergillus sensitisation was negative in all patients. In one patient (patient 1), the platelet count was above normal at the time of evaluation, and bone marrow biopsy confirmed a myeloproliferative disorder, which was treated with hydroxyurea. Patient 2 showed high circulating level of B12 vitamin, but normal level of tryptase and bone marrow examination was normal. Patient 3 had no features of a myeloid neoplasm but had venous thromboembolism a few months before the *JAK2* mutation finding. For all patients, loss of asthma control appeared less than 1 year before the diagnosis of the *JAK2* point mutation. Patients 2 and 3, routinely followed for at least 3 years, currently require low dose prednisone for control of asthma, with normal eosinophil and platelet counts.

JAK2 is a receptor-associated tyrosine kinase activated by several cytokines and growth factors [4]. In eosinophils, JAK2 is phosphorylated and activated after stimulation of the interleukin-5 receptor by the ligand and plays a major role in regulating eosinophilic development [4], migration and activation [5]. It is also involved in inhibiting apoptosis induced by granulocyte-macrophage colony-stimulating factor. A *JAK2* gene polymorphism was found associated with increased frequency of virus-induced asthma exacerbations and increased susceptibility to allergic sensitisation to environmental antigens [6]. In murine asthma models, JAK inhibitors inhibit Th2 differentiation, reduce allergen-induced airway eosinophilia, and prevent airway hyper-responsiveness, mucus hypersecretion and Th2 cytokine production [7, 8].

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Hypereosinophilia (blood eosinophil count >1500 per mm^3) in asthma patients may hide some rare myeloid or lymphoid neoplasms. Their identification has prognostic and therapeutic relevance because of the potential for targeted therapy. http://bit.ly/2JCoVIA

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TABLE 1 Clinical characteristics of three patients with asthma and hypereosinophilia

	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Male
Age at asthma onset years	15	6	6
Age at asthma loss of control years	36	54	62
Age at *JAK2* mutation diagnosis years	38	55	65
Atopy	Yes	Yes	Yes
FEV_1 % pred	43	80	90
Blood eosinophil maximum count per mm^3	5540	4510	2000
Platelet count per mm^3	670 000	315 000	320 000
Haemoglobin level $g \cdot dL^{-1}$	15	13.5	16.6
Bronchoalveolar lavage			NA
Total cell count per mL	340 000	260 000	
Macrophages %	15	10	
Lymphocytes %	5	0	
Neutrophils %	5	5	
Eosinophils %	75	85	
Lung CT scan	Bilateral infiltrates	Bilateral infiltrates	Infiltrates in right middle lobe
Other organ involved	Chronic urticaria, radial artery thrombosis	None	Recurrent pulmonary embolism and deep vein thrombosis
Vitamin B12 level# $pmol \cdot L^{-1}$	1200	810	NA
T-cell clone in peripheral blood	No	Yes	No
Bone marrow biopsy results	Myeloproliferative disorder	Normal	Normal
Actual treatment	Hydroxyurea Prednisone 10 mg per day Warfarin High-dose ICS	Prednisone 9 mg per day High-dose ICS	Prednisone 10 mg per day High-dose ICS Warfarin
Last blood eosinophil count under treatment per mm^3	290	330	300

FEV_1: forced expiratory volume in 1 s; CT: computed tomography; ICS: inhaled corticosteroid therapy. #: normal values 139–651 $pmol \cdot L^{-1}$.

The *JAK2* mutation p.Val617Phe (V617F) induces a constitutively active protein and leads to myeloproliferation. The *JAK2* V617F point mutation is found in 27% of cases of chronic myeloproliferative disorder [9], mainly polycythemia vera (PV) cancer and essential thrombocythemia (ET). HE may be observed in some cases of PV and ET, with higher values observed in *JAK2* V617F-positive than -negative cases [9, 10], with the increase in granulocyte count depending on allele burden. *JAK2* mutation is also detected in 1.5% to 4% of patients with HE of unknown significance, and is associated with a poor prognosis [9, 10].

All patients in our series had childhood asthma, but loss of control appeared later, simultaneously with HE and *JAK2* mutation diagnosis. We cannot exclude an incidental finding, especially in patient 3, who currently has no features of haematological neoplasm and may have a low allele burden, which was not assessed. However, given the known role of JAK2 in eosinophil activation and asthma pathophysiology [7, 8], we consider that *JAK2* mutation, at least in our patients, may contribute to increased blood eosinophilia count and therefore asthma severity.

In our centre, we did not find any other haematological neoplasm associated with HE, probably because of recruitment bias, since haematological disorders with HE are rarely associated with localised disease such as asthma or eosinophilic pulmonary infiltrates at disease onset. For example, in a small series of 18 asthma patients with HE, only one had a clonal T-cell receptor-gamma rearrangement [11]. One case of severe asthma in a child revealing a lymphoid variant of HE syndrome has been reported [12].

Our case series, with the limitation of bias due to its retrospective design, emphasises that HE in severe asthma patients may hide some rare haematological neoplasms, with lung manifestations as a single organ involvement. Blood eosinophilia >2000 per mm^3, pulmonary infiltrates, persistence of high blood eosinophil counts under oral steroids, history of venous or arterial thrombosis, or increased platelet count should signal a possible haematological neoplasm and trigger a thorough evaluation.

This evaluation seems important because in patients with severe asthma, new biological therapies targeting the Th2 response specifically target disease with increased blood eosinophil count [13]. Mepolizumab has demonstrated clinical benefit in conditions with high eosinophil count other than asthma, such as HE

syndrome [14] and eosinophilic granulomatosis with polyangiitis [15]. Despite the rarity of those molecular aberrations, their identification has prognostic and therapeutic relevance because of the potential for targeted therapy with JAK inhibitors [5, 7]. In patients with severe asthma and recurrent HE, screening for lympho- or myeloproliferative disorders (at least blood smear examination, tryptase and vitamin B12 dosage [3]) should be part of the evaluation.

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References

1 Price DB, Rigazio A, Campbell JD, *et al.* Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015; 3: 849–858.
2 Weissler JC. Eosinophilic lung disease. *Am J Med Sci* 2017; 354: 339–349.
3 Groh M, Pagnoux C, Baldini C, *et al.* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015; 26: 545–553.
4 Watanabe S, Arai Ki. Roles of the JAKSTAT system in signal transduction via cytokine receptors. *Curr Opin Genet Dev* 1996; 6: 587–596.
5 Monahan J, Siegel N, Keith R, *et al.* Attenuation of IL-5-mediated signal transduction, eosinophil survival, and inflammatory mediator release by a soluble human IL-5 receptor. *J Immunol* 1997; 159: 4024–4034.
6 Tripathi P, Hong X, Caruso D, *et al.* Genetic determinants in the development of sensitization to environmental allergens in early childhood. *Immun Inflamm Dis* 2014; 2: 193–204.
7 Kudlacz E, Conklyn M, Andresen C, *et al.* The JAK-3 inhibitor CP-690550 is a potent anti-inflammatory agent in a murine model of pulmonary eosinophilia. *Eur J Pharmacol* 2008; 582: 154–161.
8 Ashino S, Takeda K, Li H, *et al.* Janus kinase 1/3 signaling pathways are key initiators of TH2 differentiation and lung allergic responses. *J Allergy Clin Immunol* 2014; 133: 1162–1174.e4.
9 Jones AV, Kreil S, Zoi K, *et al.* Widespread occurrence of the JAK2 V617F mutation in chronic myeloproliferative disorders. *Blood* 2005; 106: 2162–2168.
10 Schwaab J, Umbach R, Metzgeroth G, *et al.* KIT D816V and JAK2 V617F mutations are seen recurrently in hypereosinophilia of unknown significance. *Am J Hematol* 2015; 90: 774–777.
11 Freymond N, Kahn J-E, Legrand F, *et al.* Clonal expansion of T cells in patients with eosinophilic lung disease. *Allergy* 2011; 66: 1506–1508.
12 Leu T, Rauthe S, Wirth C, *et al.* Ein T-Zell assoziiertes Hypereosinophilie-Syndrom (L-HES) als Differenzialdiagnose eines Asthma bronchiale [The lymphoid variant of HES (L-HES) as differential diagnose of severe asthma in childhood]. *Klin Padiatr* 2016; 228: 319–324.
13 Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017; 377: 965–976.
14 Kuang FL, Fay MP, Ware J, *et al.* Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. *J Allergy Clin Immunol Pract* 2018; 6: 1518–1527.
15 Wechsler ME, Akuthota P, Jayne D, *et al.* Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; 376: 1921–1932.