Supplementary material for
Use of Ruxolitinib in COPA syndrome manifesting as life-threatening alveolar hemorrhage

Supplementary Table 1: Patient presentation and literature review of COPA syndrome cases

Abbreviations: ILD, Interstitial Lung Disease; GGO, Ground Glass Opacities; ANA, antinuclear antibodies; ANCA, Antineutrophil cytoplasmic antibodies, RF, Rheumatoid factor; CCP, Cyclic citrullinated peptide antibodies; SM, anti-Smith antibodies; NSAID, Non-steroidal anti-inflammatory drugs

	Watkin et al. 2015[1] ***Vece et al. 2016***[2] ***Tsui et al. 2018***[3]	***Noorehalhi et al. 2018***[4]	***Jensson et al. 2017***[5]	***Volpi et al. 2018***[6]	*Taveira-DaSilva et al. 2018*[7]	***Boulisfane-El Khalifi et al. 2019***[8]	***This study***
Families/Individuals carrying the mutation	5/30	1/1	1/3	1/1	1/4	1/5	1/2
Symptomatic carriers	21/30	1/1	3/3	1/1	4/4	4	1/2
Female	13 (62%)/14	-	2/2	1/1	2/2	1/4	1/2
Male	8 (38%)/16	1/1	1/1	-	2/2	3/4	-
Age of onset	16 (76%) < 5 years	5 years	32, 1.5, 11 years	3 years	1, 16, 26, 56 years	10 years	2 years
Lung disease	21 (100%)	1 (100%)	3 (100%)	1 (100%)	4 (100%)	2 (50%)	1 (100%)
ILD		Yes		Yes	Yes	Yes	Yes
Alveolar haemorrhage		Yes		-	-	Yes	Yes
Lung carcinoma		-		-	1 (25%) at age 56	No	-
CT-scan findings	GGO Reticulations Traction cysts Nodules	GGO Septal thickening Traction cysts	-	GGO Septal thickening Traction cysts	Diffuse interstitial infiltrative lesions Cystic lesions	-	Patchy alveolar opacities Traction cysts
Pathological findings	Follicular bronchiolitis Interstitial lymphoid	-	Follicular bronchiolitis Interstitial lymphoid infiltrate Emphysema / Cysts	-	Follicular bronchiolitis Peribronchovascular and subpleural lymphoid follicles	_	Alveolar haemorrhage Respect of the parenchymal structure Thin alveolar walls

	Infiltrate / nodules CD20+ B cells and CD4+ and CD8+ T cells Interstitial fibrosis Emphysema / Cysts Capillaritis Alveolar haemorrhage		Neuroendocrine cell hyperplasia		Emphysema / Cysts Neuroendocrine cell hyperplasia		No fibrosis No sign of capillaritis Lymphoid nodules
Joint disease	20 (95%) Juvenile idiopathic arthritis, rheumatoid arthritis, polyarticular arthritis affecting large joints (shoulders, knees) and small joints (metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints, cervical spine disease)	1 (100%) Temporomandibular arthropathy	3 (100%)	1 (100%) Severe, cervical, hands and feet	2 (50%)	2 (50%) Transient arthralgia of the knee without joint lesions or synovitis 1	-
Kidney disease	Fibrosing glomerulonephritis: 4	-	-	-	Nephrolithiasis: 1 Renal carcinoma: 1	Lupus nephritis: 1	-
Other organ involvement	Autoimmune thyroitidis: 1 Strokes: 2	-	Skin rash, suspicion of erythema multiforme: 1	-	Neuromyelitis optica: 1	Facial oedema	-
Positive autoantibodies	18 (86%)	1 (100%)	3 (100%)	1 (100%)	3 (75%)	Available for 1	1 (100%)
ANAs	14 (67%)	1 (100%)	3 (100%)	1 (100%)	-	0 (0%)	-
ANCAs	15 (71%)	-	-	-	1 (25%)	0 (0%)	-
RF	9 (43%)	1 (100%)	3 (100%)	1 (100%)	1 (25%)	-	1 (100%)
CCP	-	1 (100%)	2 (66%)	-	-	-	-

SM	-	-	-	-	-		1 (100%)
Other immunologic features		High C3, HLAB27					CD8 and NK lymphopenia
COPA Mutation	p.(Lys230Asn) (n=1) p.(Arg233His) (n=2) p.(Glu241Lys) (n=1) p.(Asp243Gly) (n=1)	p.Trp240Arg	p.Glu241Lys	p.Arg233His	p.Arg233His	p.Arg233His	p.Arg233His
Corticosteroids	21 (100%)	-	3 (100%)	1 (100%)	1 (25%)	1 (ND)	1 (100%)
Immunosuppressive drugs	Cyclophosphamide Rituximab Methotrexate Adalimumab Azathioprine	Ethanercept Methotrexate	Azathioprine: 1 Mycophenolate mofetil: 3 Methotrexate: 2 Anti-TNF: 1	Methotrexate Anti-TNF Abatacept		Cyclophosphamide Mycophenolate mofetil	Hydroxychloroquin Azathioprine Mofetil mycophenolate Cyclophosphamid Ruxolitinib
Anti-inflammatory drugs (NSAIDs)	Naproxen		Salazopyrin: 3				
Lung transplantation	2		2				

Supplementary Figure 1: Surgical lung biopsy. At low magnification (A), hematoxylin & eosin staining show a heterogeneous repartition of the lesions. (B) The parenchymal structure is preserved with thin alveolar walls and no vasculitis nor pulmonary arterial hypertension signs. (C) The alveolar walls are thin with no inflammatory infiltrate, there is no sign of lung fibrosis. The biopsy showed also very rare lymphoid nodules.

Supplementary Figure 2: Pedigree of the affected patient

The index patient is marked by an arrow. Individuals carrying the heterozygous c.698G>A p.(Arg233His) *COPA* mutation are identified by p.[(Arg233His)];[=]. Individuals with no *COPA* mutation are identified by p.[=];[=].

Supplementary Figure 3: Constitutive activation of the type I IFN signaling observed in the patient before treatment and her mother

(A) and (B) Increased constitutive phosphorylation of STAT1 (A) and STAT3 (B) in CD3+, CD4+ and CD8+ lymphocytes from the patient compared to a healthy control (HC).

(C) IFN score calculated from the median fold change in relative quantification values of a set of 6 ISGs (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2*, *SIGLEC1*, normal < 2.466) recorded in the peripheral blood from the patient before treatment, the patient's mother (Pt's mother), and healthy controls (HC).

(D) Concentrations of IFNα protein assessed by ultra-sensitive digital ELISA in plasma or serum from the patient before starting treatment with ruxolitinib, the patient's mother (Pt's mother) and healthy controls (HC, values < 10 fg/mL) [9,10].

(E) Increased constitutive phosphorylation of STAT1 in CD3+, CD4+ and CD8+ lymphocytes and monocytes from the patient's mother (Pt's mother) compared to a healthy control (HC).

Supplementary References

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