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Clinical spectrum and therapeutic management of auto-immune myelofibrosis: a nation-wide study of 30 cases

In 2003, Pullarkat *et al.* described for the first time “primary autoimmune myelofibrosis” (AIMF) as myelofibrosis occurring in patients presenting autoimmune biological signs in the absence of a well-defined autoimmune disease (AID).¹ Conversely, the term “secondary AIMF” is used for myelofibrosis occurring with a well-defined AID, most commonly systemic lupus erythematosus (SLE) but also systemic sclerosis, dermatomyositis, Sjögren syndrome, or organ-specific autoimmune diseases such as autoimmune hepatitis.

Being able to differentiate between an autoimmune or a clonal disease is crucial because of different therapeutic management, but can remain challenging. Since the discovery of gain of function (GOF) mutations of Janus kinase 2 (*JAK2*), novel findings such as calreticulin (*CALR*) GOF mutation and mutant myeloproliferative leukemia (*MPL*) protein have been described in clonal myelofibrosis. Interestingly, these findings seem to lack in case of autoimmune disease. Moreover, one of the fundamental characteristics of AIMF seems to be its sensitivity to glucocorticoids (GC),² therefore GC remain the first-choice therapy. However, the long-term complications of GC are severe, and other GC-sparing therapies should be considered. Unfortunately, little is known about the natural course of the disease and the optimal indications and efficacy of treatments.

The main goal of this study was to describe the presentation, the indications of current treatment and the course of 30 multicenter AIMF cases in France.

We performed a nation-wide, retrospective, and observational study of AIMF by contacting two French networks, the “Club Rhumatismes et Inflammation” (CRI) and “Maladies rares immuno-hématologiques” (MaRIH), dedicated to autoimmune diseases and rare immunohematologic diseases, respectively. Primary or secondary AIMF cases had to fulfill the following criteria to be included in the study: bone marrow (BM) fibrosis proven by BM biopsy, regardless of grade AND a defined AID according to current respective American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) international classification criteria OR autoimmune cytopenia OR positive ANA detection (> 1:80 titers). Cases were excluded if the myelofibrosis could be explained by another condition (hematological disorder, solid neoplasia, chronic infection, toxic exposure known to induce myelofibrosis, radiotherapy, metabolic). All observations were reviewed by a steering committee consisting of an internist and a rheumatologist specialized in the care of rare auto-immune disorders (TM and LA), and data were collected by using a standardized and anonymized data form. Detailed clinical and biological characteristics of the 30 cases are shown in Table 1.

The presence of cytopenias at diagnosis of AID or onset during follow-up is not rare, and is mostly due to iron or vitamin deficiencies, chronic inflammation or autoimmune cytopenias. In our study, AIMF was diagnosed during follow-up consultation for a known AID (mostly SLE and portosystemic shunts [pSS]) in 40% of cases, which strengthens the need to explore any new hematological abnormalities during follow-up and suggests the need for screening for AIMF at any time. Moreover, 50% of the cases for which geographic origin was available (22 of 30 patients) were of African or

Table 1. Clinical and biological characteristics of cases at the time of autoimmune bone marrow fibrosis diagnosis (n=30).

Characteristics	
Sex	
Male	6 (20%)
Female	24 (80%)
Geographic origin (n=22)	
European	9 (41%)
Afro-American	7 (32%)
North-African	4 (18%)
Asian	2 (9%)
Age at diagnosis (years), median (IQR)	
AIMF	37 (30–49)
AID	31 (24–42)
Median delay between diagnosis of AIMF and AID (years), median (IQR)	0 (0–7)
Known AID before AIMF onset	12 (40%)
Median hemoglobin level (g/L) at AIMF diagnosis, (IQR)	94 (79–106)
Median platelet count (10 ⁹ /L) at AIMF diagnosis, (IQR)	90.5 (75–182)
Median WBC count (10 ⁹ /L) at AIMF diagnosis, (IQR)	
Leukocytes (n=30)	2.65 (1.8–4)
Neutrophils (n=29)	1.36 (0.85–2.17)
Lymphocytes (n=29)	0.74 (0.5–1.1)
Hypocomplementemia	18 (60%)
Positive Coombs test (Coombs test availability n=25)	13 (52%)
Primary auto-immune myelofibrosis	0 (0%)
Secondary auto-immune myelofibrosis	30 (100%)
Associated reported AID	
Systemic lupus erythematosus	21 (70%)
Primary Sjögren syndrome	5 (17%)
McDuffie vasculitis	1 (3%)
Mixed connective tissue disorder	1 (3%)
Dermatomyositis	1 (3%)
Immune thrombocytopenic purpura	1 (3%)
Fibrosis grade in bone-marrow biopsy (n=28)	
Grade 1	18 (64%)
Grade 2	9 (32%)
Grade 3	1 (4%)
Available mutation status (n=11)	
<i>JAK2</i> negative	7
<i>JAK2</i> and <i>CALR</i> negative	1
Triple negative (<i>JAK2</i> ; <i>MPL</i> and <i>CALR</i>)	3

AIMF: autoimmune myelofibrosis; AID: associated autoimmune disease; IQR: Interquartile range; WBC: white blood cell;

North-African origin, which could suggest that AIMF could be more frequent in these patients.

The presence of ANA is commonly described in patients with early-developing primary myelofibrosis⁴ but can be positive at titers of 1:80 in up to 13% of healthy individuals aged 21 to 60 year.⁵ Physicians should be aware of this important element as the presence of ANA does not necessarily indicate that myelofibrosis is secondary to an autoimmune process. Moreover, one should not neglect the possibility of having a true primary myelofibrosis occurring during the course of an AID as some studies have described a 20% increased risk for the development of an myeloproliferative neoplasms in patients with auto-immunity.⁶

Mutational status was negative for all screened cases

Table 2. Treatment response and analysis of hematological response of primary autoimmune myelofibrosis after treatment (based on 2013 revised Tefferi *et al.*³ response criteria for myelofibrosis) (n=30)

Treatment line for AIMF and nature	Number of cases N (%)	Treatment response			
		CR	CR lacking CBMB	PR	NR
Global response	29 (100)	2	16	5	6
First-line therapy			29 (100)		
GC alone	4 (14)	1	0	3	0
HCQ alone	2 (7)	0	0	0	2
GC + HCQ	7 (24)	0	5	1	1
GC + cytoreductive agents and GF	1 (3)	0	0	0	1
GC + IS	3 (10)	1	2	0	0
GC + HCQ + IS	12 (41)	0	9	1	2
Second-line therapy			7 (23)		
+ other IS	6 (86)	0	3	2	1
Splenectomy	1 (14)	0	0	1	0
Third-line therapy			2 (7)		
+ other IS	2 (100)	0	1	0	1
Hematological response N (%)					
Global response					
Complete response				2 (7)	
Complete response lacking CBMB				16 (55)	
Partial response				5 (17)	
Persistent splenomegaly				1/5 (20)	
Persistent neutropenia				2/5 (40)	
Persistent anemia				1/5 (20)	
Persistent thrombocytopenia				1/5 (20)	
No response				6 (20)	
Not applicable because of therapeutic abstention				1 (3)	
Symptom response					
Anemia response (hemoglobin level increase ≥ 20 g/L)				21/29 (72%)	
Spleen response (palpable spleen becoming non-palpable)				MD/7	
Clinical improvement (by physician's assessment)				10/13 (77%)	
AIMF evolution (n=29)					
Stable disease				23 (79%)	
Relapse				6 (21%)	

AIMF: autoimmune myelofibrosis; CR: complete response i.e., correction of cytopenia and symptoms; GC: glucocorticoids; GF: growth factors; HCQ: hydroxychloroquine; IS: immunosuppressive therapy; CBMB: confirmatory bone marrow biopsy; MD: missing data.

(n=11). This is an important finding because the lack of typical *JAK2*, *CALR* and *MPL* mutations could be considered a diagnostic criterion, and to our knowledge this is the first time that these data are available for more than 25% of cases examined. The search for clonal mutations (*JAK2*, *CAL-R*, *MPL*) should be mandatory with suspected AIMF, and one could speculate that patients with triple negative (*JAK2*, *CAL-R*, *MPL*) that also have other negative clonal markers (e.g., *ASXL1*, spliceosome or abnormal karyotype) might in fact be misdiagnosed AIMF. However, little is known about the pathophysiology of AIMF and the possibility of a driver role of yet unknown mutations (as seen in aplastic anemia) should not be dismissed.

As reported in the literature, myelofibrosis in all 30 cases consisted of reticulin fibers, and no collagen fibrosis was described.^{7,8} This characteristic could also allow for differentiating AIMF from clonal processes, in parallel with the reported absence of megakaryocyte dysplasia.^{8,9} In Table 3 the principal differences between myeloproliferative disorder and AIMF are summarized to provide guidance for the diagnosis.

We used the adapted Tefferi *et al.* revised 2013

response criteria for myelofibrosis³ to evaluate outcome and response to therapy. These response criteria were initially designed to evaluate the response to a malignant clonal disease and required a confirmatory BM biopsy to qualify for complete response (CR). Cytopenias were defined according to these criteria. Moderate, severe and deep thrombocytopenia were defined by platelet count of respectively 149–50 g/L, 49–20 g/L or <20 g/L. Moderate, severe and deep neutropenia were defined by neutrophil count of respectively 1.4–1 g/L, 0.9–0.5 g/L and <0.5 g/L. Lack of complete clinical and biological response to treatment was defined as partial response (PR) criterion. Correction of cytopenia and symptoms was defined as CR, but correction of cytopenia and symptoms without a confirmatory BM biopsy (CBMB) for correct qualification was defined as “CR lacking CBMB”.

Among the 30 cases, treatment was required because of AIMF manifestations in 29 patients and therapeutic abstention was considered for one patient. The detailed therapeutic strategy was available for all 29 treated cases. GC were prescribed as first-line therapy in 27 of 29 cases: alone in 5 of 27 and in combination with immunosup-

Table 3. Comparison between autoimmune myelofibrosis and myeloproliferative disorder presentation

Characteristics	AIMF	Myeloproliferative disorder ⁸⁻¹⁰
Median age, IQR (years)	37 (30–49)	66 (14-92)
Female (%)	80	39
Clinical presentation		
Constitutional symptoms	+	+
Splenomegaly	Absent or mild	+
Cytopenias at diagnosis		
Median hemoglobin level (g/L), (IQR)	94 (79–106)	100 (50-161)
Median platelet count (10 ⁹ /L), (IQR)	90.5 (75–182)	209 (6-2466)
Median leukocyte count (10 ⁹ /L), (IQR)	2.65 (1.8–4)	9 (1-147)
Presence of		
Tear drop cells	+/-	+
Leukoerythroblastosis	+/-	+
Eosinophilia	-	+/-
Basophilia	-	+/-
Biological autoimmune indicators (ANA, RF, hypergammaglobulinemia)	Yes	Yes (early stages)
Bone marrow features		
Reticulin fibrosis	Predominant	Yes (early stages)
Collagen fibrosis	Absent	Predominant
Osteosclerosis	Absent	+/-
Cellularity	Mostly hypercellular	Variable according to stage: hypercellular in early pre-fibrotic stages, normo or hypo-cellular in fibrotic stages
Megakaryocyte dysplasia	Absent	MK atypia and clustering
Intrasinusoidal hematopoiesis	Subtle	++
Lymphoid infiltrates	++ (non-paratrabeular lymphoid aggregates)	+/-
Plasma cells	Mild polyclonal non-IgG4 plasmacytosis	-
Mutational features		
Mutational features JAK ^{V617F}	Negative	Positive (90%) 60%
CAL-R		20–25%
MPL		5–10%

AIMF: autoimmune myelofibrosis; ANA: antinuclear antibodies; IQR: Interquartile range; MK: megakaryocyte; RF: rheumatoid factor.

pressive agents in 15 of 27. A second-line therapy was indicated because of incomplete response of AIMF in 7 of 29 (23%) cases and a third-line therapy in 2 of 29 (7%). For all treatment lines combined, the most frequent immunosuppressive agents associated with GC were mycophenolate mofetil (5 of 29 cases), methotrexate (4 of 29 cases) and rituximab (4 of 29 cases). Considering only cases with CR or CR lacking CBMB, the most common immunosuppressive agents were mycophenolate mofetil (4 of 18), azathioprine (3 of 18) and intravenous immunoglobulins (3 of 18). Six patients were considered as non responders, and did not present any particular clinical, hematological or anatomopathological characteristics. The analysis of treatment response by treatment line is reported in Table 2. Among the 27 cases receiving GC, 18 (67%) showed CR or CR lacking CBMB. Overall, 15 patients (data available for 25 of 29 treated patients) (55,5%) cases showed GC dependency, and GC cessation was achieved in the remaining 10 (40%) with the help of immunosuppressive GC-sparing agents in only 6 of 10.

Median follow-up time was 28.5 months (range: 1 month to 18.5 years; follow-up data available for 26 of 29 cases). Six cases presented ≥ 1 relapse (1 due to treatment

discontinuation by the patient) (Table 2).

Treatment complications were reported for 9 of 18 cases and were mainly attributed to GC therapy. Four of the cases exhibited vascular and cutaneous fragility, three opportunistic infections (one case of pulmonary tuberculosis, one of pneumocystis pneumonia leading to death, one without further details) and cushing-like appearance, obesity, arterial hypertension and glucocorticoid-induced diabetes in one case each.

In the absence of available response criteria for AIMF, we used an adaptation of the 2013 revised International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Leukemia Net (ELN) response criteria for myelofibrosis³ to evaluate treatment response. However, in our cases, a confirmatory BM biopsy was rarely performed, legitimately because of the normalization of the blood panel in response to immunosuppressive therapy and an obvious non-malignant context. Hence, only two cases in our study qualified for CR according to Tefferi *et al.* criteria,³ but 18 cases showed complete improvement of hematological complications and symptom response without a confirmatory BM biopsy (CR lacking CBMB). The Tefferi *et al.* response

criterion allowed us to objectively assess response to immunosuppressive therapy but requires further adaptation in the context of an AID to be fully relevant. Nevertheless, most cases (27 of 29 treated patients) received GC alone or combined with other immunosuppressive agents as first-line therapy, which allowed for CR or CR lacking CBMB in more than 60% of cases. These findings seem to suggest that GC remain the first-choice therapy because of response in more than 50% of cases, but a high rate of GC dependency and long-term complications indicate a need to find new sparing drugs.

In case of persistent neutropenia and anemia, no infectious complications seemed to occur and no transfusion dependency was observed, so treatment escalation with additional immunomodulatory or immunosuppressive agents may not be indicated in these cases. In contrast, persistent thrombocytopenia might indicate a specific treatment because of persistent risk of hemorrhagic syndrome.

In conclusion, this analysis of 30 unique French cases of AIMF is the largest to date. These findings may help improve early diagnosis of this rare disease and allow for improvement and homogenization of the set of therapeutic tools to be used in future studies.

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