Autoimmune myelofibrosis associated with Sjogren's syndrome successfully treated with steroids and improved myelofibrosis

Seiji Kakiuchi, Ikumi Takagi, Hiroaki Akiyama, Hiroyuki Matsuba, Junpei Rikitake, Nobuko Iwata
Department of Hematology, Yodogawa Christina Hospital, Osaka, Japan

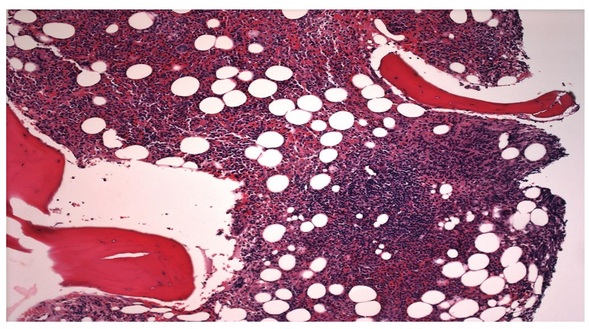
Introduction

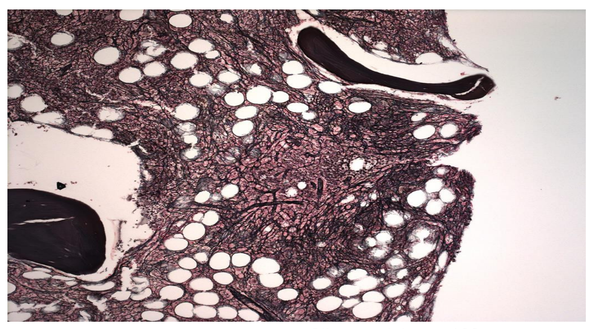
Myelofibrosis is a disease that causes widespread bone marrow fibrosis as a result of the proliferation of reticulum fibers, collagen fibers, and bone marrow fibroblasts. There are two types of myelofibrosis: primary myelofibrosis of unknown cause (PMF) and secondary myelofibrosis secondary to other diseases. Of the two, secondary myelofibrosis that occurs secondary to autoimmune abnormalities is termed as autoimmune myelofibrosis (AIMF). Here, we describe an extremely rare case report, where myelofibrosis was treated with steroids in autoimmune myelofibrosis concomitant with Sjogren's syndrome.

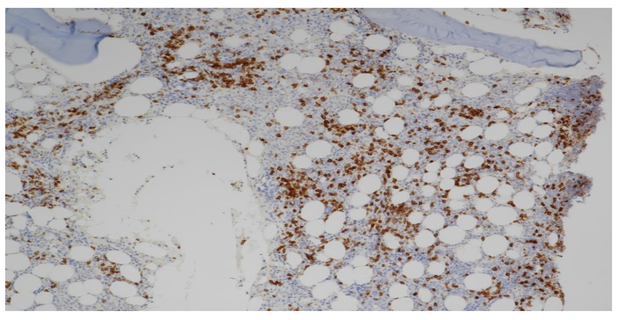
Case Presenatation

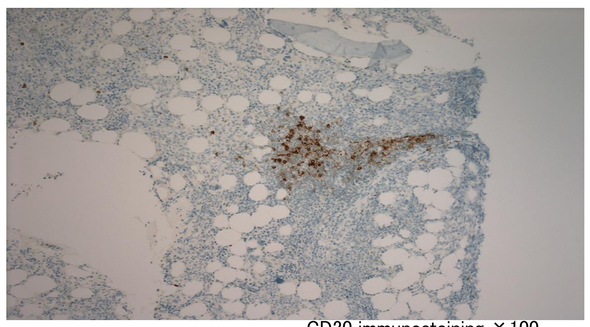
【Case Presentation】A 49-year-old Japanese man observed oral and epistaxis bleeding three days ago and visited our hospital. Blood test revealed a platelet count of 1 × 10^9/l, and he was hospitalized. The patient has long been aware of the Raynaud phenomenon, though the duration was unknown. Examination 8 months before the visit revealed no abnormalities other than a slight decrease in the platelet count to 110 × 10^9/l.
【Past History】None 【Allergy】None 【Medication】None
【Famiry History】Elderly sister Sjogren's syndrome
【Review of System】 Smoking : 20/day × 29 years Alcohol : None
【Physical Examination】
Blood Pressure 133/96 mmHg, Heart Rate of 109 beats per minute, Respiratory Rate of 16 per minute, Body temperature of 37.4℃. Hepatospleen and body lymph nodes were not palpable
Petechiae were present on the buccal mucosa and limbs

Bone Marrow Examination
hyperplastic bone marrow, and the number of megakaryocytes increased slightly to 44 cells/mm^2; however no atypia or aggregation was observed.


HE staining × 100

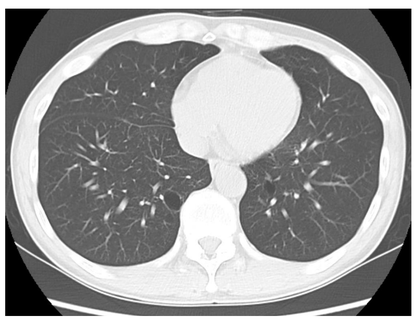

Silver staining × 100

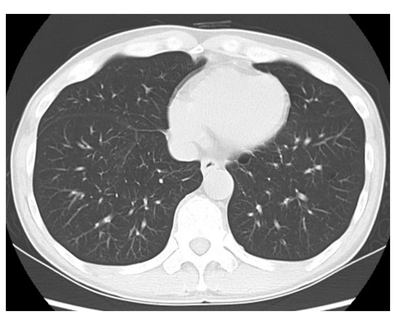

CD3 immunostaining × 100


CD20 immunostaining × 100

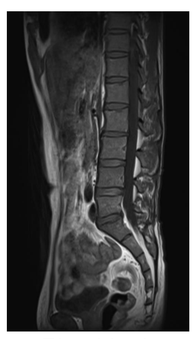
Complete Blood Count				Blood chemistry/Serological test			
WBC	6,500/μl	AST	34 U/l	Haptoglobin	46 mg/dl		
Neu	53%	ALT	19 U/l	MPO-ANCA	1.0> U/l		
Lym	36%	LDH	398 U/l	PR3-ANCA	4.6 U/ml		
Mon	10%	γGTP	38 U/l	Lupus anticoagrant	1.16		
Eos	0%	ALP	248 U/l	CH50	12 mdl		
Bas	1%	T.Bil	1.02 mg/dl	C4	54 mg/dl		
RBC	499×10^4/μl	TP	8.7 g/dl	C3	85 mg/dl		
Hb	14.3 g/dl	Alb	4.4 g/dl	RF	200 IU/ml		
MCV	88.6 fl	CK	84 U/l	anti nucleolar antibody	×1280		
Ht	44.2%	BUN	10.3 mg/dl	anti ds-DNA andibody	10> IU/ml		
Plt	0.1×10^4/μl	Cr	0.82 mg/dl	anti Sm antibody	(-)		
IPF	3.4%	CRP	0.1 mg/dl	anti RNP antibody	(-)		
Erythroblast	(-)	Fe	119 μg/dl	anti SS-A antibody	×256		
Tear drop	(-)	Ferritin	387.3 ng/ml	anti SS-B antibody	×1		
		IgG	2552 mg/dl	anti SCL-70 antibody	(-)		
Coagulation		IgA	509 mg/dl	anti centromere antibody	(+)		
PT-INR	1.05	IgM	91 mg/dl	anti CCP antibody	0.6> U/ml		
APTT	26.5 sec	TSH	2.92 μIU/ml	PAIgG	3240 ng/10^7cells		
Fibrinogen	321 mg/dl	FreeT4	1.17 ng/dl	anti *H.Pylori* antibody IgG	3> U/ml		
FDP	2.6 μg/ml	Vit.B12	227 pg/ml	Thrombopoietin	3.84 fmol/l		
D-dimer	0.82 μg/ml	Follic acid	3.7 ng/ml	sIL-2R	917 U/ml		

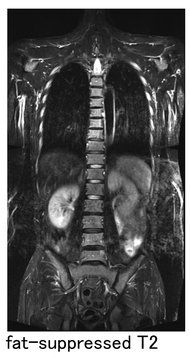
	Prior treatment	Post Treatment	Normal
TGFβ1 (ng/ml)	1.75	1.80	1.56-3.24





Thoracoabdominal CT
a cyst in the lung field and no hepatosplenomegaly


T1-weighted

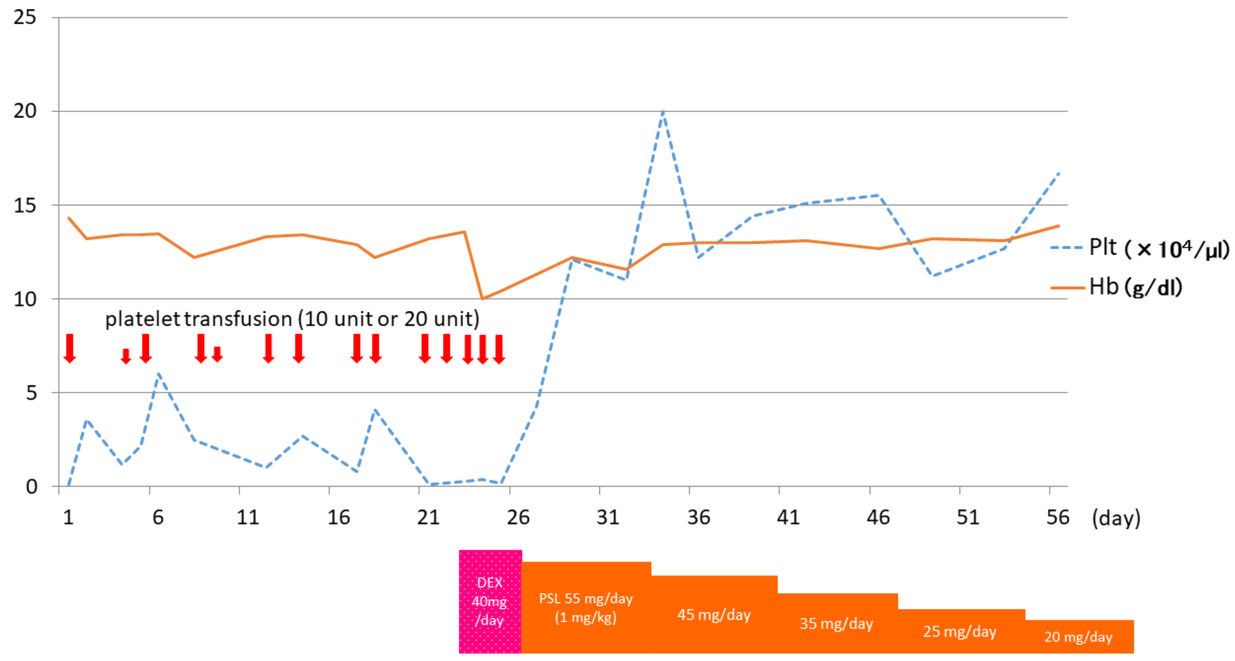

fat-suppressed T2 weighted

Whole spine MRI
Hyperplastic marrow

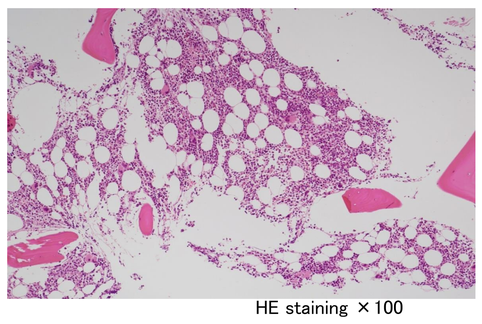
Shirmer's test below 5 mm/5 min **Fluorescein test** positive

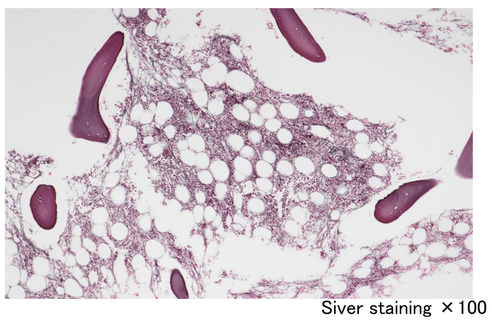
Final Diagnosis : Autoimmune Fibrosis associated with Sjogren's Syndrome

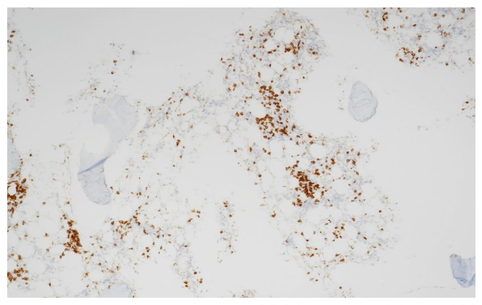
Clinical Course

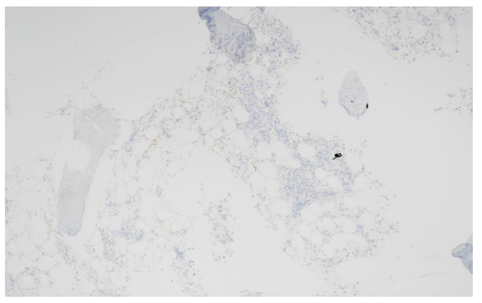


Bone marrow examination on day 182
Aspiration was possible. Silver staining showed improved fibrosis to MF-0


HE staining × 100


Siver staining × 100


CD3 immunostaining × 100


CD20 immunostaining × 100

Discussion

Features	AIMF	PMF
Peripheral blood smear		
Dysplasia	-	-
Tear drop cells	+/-	+
Leukoerythroblastosis	+/-	+
Eosinophilia	-	+/-
Basophilia	-	+/-
Bone marrow		
Reticulin fibrosis	MF-1	MF-2 to 3 in fibrotic stage
Osteosclerosis	-	+/-
Cellularity	mostly hypercellular	typically hypercellular
		in prefibrotic stage, hypocellular
		in fibrotic stage, normocellular
Dysplasia	-	megakaryocytic proliferation and atypia
Hyperplasia	erythroid and megakaryocytic lineages	granulocytic and megakaryocytic lineages
Intrasinusoidal hematopoiesis	+/-	+
Lymphoid infiltrates	+	+/-
Clinical features		
Constitutional symptoms	uncommon	common
Splenomegaly	uncommon	common
Other signs		
JAK2, CARL, or MPL mutation	-	+ (90% of cases)

+, present; -, absent; AIMF, autoimmune myelofibrosis; PMF, primary myelofibrosis

- The characteristics of AIMF are listed in Table 1. However, not all features are often present.
- Differentiation between AIMF and PMF is particularly important. The presence or absence of megakaryocyte atypia in the bone marrow, the presence or absence of lymphocytic infiltration, and the presence of splenomegaly are particularly useful. (Table 1)
- The treatment for AIMF is considered to be steroids, and it has been reported that nearly 90% of those associated with SLE respond to steroids. Those that are not steroid-responsive may benefit from immunosuppressive agents.
- The course of treatment in case reports of AIMF associated with Sjögren's syndrome was as shown in Table 2. The mechanism of fibrosis is thought to involve lymphocytes and cytokines such as TGF-β.

	Age/Sex	Initial therapy	Hematological response	Bone marrow response	Reccurence	Maintenance therapy
1. Gruson et al.	30/F	PSL 1 mg/kg/day for 1 month → tapered off over next 3 months	(+)	ND	(+) at 5 months	Normalized within 2 weeks after azathioprine administration
2. Hattori et al.	72/F	PSL 1 mg/kg/day (50 mg/body) → tapered to 10 mg in just over 2 months	(+) in 1 month	(+)	(-)	PSL 4 mg/day at 4 months
3. I.Marie et al.	59/F	mPSL 500 mg×3 days → PSL 1 mg/kg/day (70 mg/body)	(+) in 1 month	ND	(-)	PSL 15 mg/day at 12 months
4. Rizzi et al.	43/M	PSL 1mg/kg/day → tapered off over next 6 months	(+)	(-)	(+)	Restarted lowest effective dose of PSL
5. Rizzi et al.	66/F	PSL 4 mg/day + CsA 50 mg/day for 4 days every week + hydroxychloroquine 200 mg/day for 12 months	(-)	ND	ND	Hydroxychloroquine + low dose PSL

CsA, cyclosporine A; F, female; M, male; mPSL, methylprednisolone; ND, not described; PSL, prednisolone; WBC, white blood count

Marcellino B, et al. Distinguishing autoimmune myelofibrosis from primary myelofibrosis. Clin Adv Hematol Oncol. 2018 Sep;16(9):619-626. Vergara-Lluri ME, et al. Autoimmune myelofibrosis: an update on morphologic features in 29 cases and review of the literature. Hum Pathol. 2014 Nov;45(11):2183-91. Rizzi R, Pastore D,Liso A, et al Rizzi R, et al. Autoimmune myelofibrosis: report of three cases and review of the literature. Leuk Lymphoma. 2004 Mar;45(3):561-6. Marie I, Levesque H, Cailleux N, Lepretre S, Duval C, Tilly H, Courtois H. An uncommon association: Sjögren's syndrome and autoimmune myelofibrosis. Rheumatology (Oxford). 1999 Apr;38(4):370-1. Gruson B, et al. Myelofibrosis and cytopenia are not always malignant. Eur J Intern Med. 2006 Mar;17(2):136-7. Hattori N, et al. [Successful treatment with prednisolone for autoimmune myelofibrosis accompanied with Sjögren syndrome]. Rinsho Ketsueki. 2007;48(12):1539-43.

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