Diagnosis of Fanconi anemia in patients with bone marrow failure

Fernando O. Pinto,[1,2] Thierry Leblanc,[3] Delphine Chamousset,[1] Gwenaelle Le Roux,[1] Benoit Brethon,[3] Bruno Cassinat,[4] Jérôme Larghero,[5] Jean-Pierre de Villartay,[6] Dominique Stoppa-Lyonnet,[7] André Baruchel,[3] Gérard Socié,[2] Eliane Gluckman,[2] and Jean Soulier[1]

[1]Team "Genome Rearrangement and Cancer", APHP Hematology Laboratory, Hôpital Saint-Louis, Paris; INSERM U728 and U944, Hôpital Saint-Louis, Paris; and Université Denis Diderot - Paris 7, Hôpital Saint-Louis, Paris; [2]Bone Marrow Transplant Unit, Hôpital Saint-Louis, Paris; [3]Pediatric Hematology Department, Hôpital Saint-Louis, Paris; [4]AP-HP, Cell Biology Unit, Hôpital Saint-Louis, Paris; [5]APHP, Cell Therapy Unit, Hôpital Saint-Louis, Paris; [6]INSERM U768, Hôpital Necker, Paris, and [7]Department of Genetics, Curie Institute, Paris, France

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Online Supplementary Table S1. Patients with BMF likely to have an underlying inherited condition (n=30).

					Biological Diagnosis				
					PBL		Fibroblast		
Patients	Age (y)	BMF Presentation	Findings in History or PE		Increased Breaks	FANC D2	FANC D2	Hypersensitivity to MMC	Final Diagnoses
H05	M 31.7	Incidental diagnosis of BMF during w/u for URTI episodes	Neurodevelopmental delay since birth, sibling with history of BMF, low set ears, hypertelorism, 'café-au-lait' spots, arched palate, short stature		No	2	2	No	Uncategorized Inherited Syndrome
H06	F 7.3	Palor and fatigue Positive IgM for Mycoplasm	Family history of miscarriages, low birth weight, precocious puberty, height at –1.8 SD, increased AFP		No	2	2	No	Uncategorized Inherited Syndrome
H08	M 37.3	Anemia at 2yo Dyserythropoiesis at 20yo BMF on routine FBC	Consanguinity, multiple central and peripheral skeleton malformations (knee gonarthrosis, hemi-sacralization of L5, absent rib at T12, scaphoid/trapezoid fusion, dysmorphic maxilla and mandible)		No	2	2	No	Uncategorized Inherited Syndrome
H09	F 39.2	Pallor	Microcephaly, bird-headed facies, growth retardation, sister with same phenotype		No	2	2	No	Seckel syndrome
H10	M 2.5	Thrombocytopenia at 1 yo BMF on routine FBC	IUDD, microcephaly, nail dystrophy, leukoplakia, vitreous haemorrhage (Eales disease), history of false positive chromosomal breakage test on PBL		No	2	2	No	Dyskeratosis congenita (Hoyeraal-Hreidarsson)
H15	M 13.6	BMF on routine FBC	Mild reticular hyperpigmentation of skin, dystrophic nails		No	2	2	No	Dyskeratosis congenita (TERC mutated)
H16	F 14.5	New onset fatigue	No previous significant history. Physical exam with generalised hyperostosis and malformed feet. Borderline macrocrania (+2 SD).		No	2	2	No	Uncategorized Inherited Syndrome
H30	M 20.7	BMF on w/u for recurrent respiratory infections	Reticular hyperpigmentation of skin, dystrophic nails, oral mucosa leukokeratosis, absent lacrimal puncta, cleft palate, oesophageal stenosis, vesicoureteral reflux syndrome		No	2	n/a	n/a	Dyskeratosis congenita
H32	F 22.9	Anemia at 14 yo, marrow dysplasia at 18 yo, BMF on routine FBC	1 café-au-lait spot, low-set ears, oral mucosa leukokeratosis, cutaneous hyperkeratosis with hypochromia, hyper IgA, malrotated kidney, short stature		No	2	2	No	Uncategorized Inherited Syndrome
H38	F 47.5	See Table 3	See Table 3		No	2	1	Yes	Fanconi Anemia[§]
H39	F 1.6	Bicytopenia at birth	Large forehead, developmental delay, height at –1.7 SD		No	2	2	No	Uncategorized Inherited Syndrome
H44	F 6.4	Non-hemolytic anemia since birth	Thumb malformation, short stature, isolated erythroblastopenia in bone marrow evaluation		No	2	n/a	n/a	Diamond-Blackfan

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H47	F	40.5	Incidental diagnosis of bicytopenia at 31 yo BMF on routine FBC	History of gluten intolerance and hyperprolactinemia, brother w/ MDS, history of previous false positive chromosomal breakage test on PBL	No	2	2	No	Uncategorized Inherited Syndrome
H49	F	0.8	Non-hemolytic anemia at birth, BMF on routine FBC	IUDD and developmental delay Normal physical exam	No	2	2	No	Uncategorized Inherited Syndrome
H51	F	8.9	Mild bicytopenia at 2 yo BMF on routine FBC	Prematurity, cardiac septal defect, poikilodermia, dystrophic nails, two siblings with same phenotype, short stature	No	2	n/a	n/a	Dyskeratosis congenita
H53	F	7.5	HSCT for AA at 4 yo BMF on routine FBC	Prematurity, microcrania, metopic craniosynostosis, 2 other siblings affected (one developed MDS), short stature	No	2	2	No	Uncategorized Inherited Syndrome
H57	F	13	Mild cytopenia since birth BMF on routine FBC	Sister with a history of BMF and suspicion of immunodeficiency (disseminated mycobacteriosis), increased HbF, one 'café-au-lait' spot	No	2	2	No	Uncategorized Inherited Syndrome
H60	F	11.6	See Table 3	See Table 3	No	2	2	Yes	Fanconi Anemia[§]
H65	M	12.7	Incidental diagnosis during w/u pre-myringoplasty (for recurrent otitis)	Low-set ears, hypotelorism, microphtalmia, pubertal delay, alopecia, brittle/dry hair, palmar hyperkeratosis, arachnodactily, poor dentition	No	2	n/a	n/a	Uncategorized Inherited Syndrome
H66	F	15.4	BMF on routine FBC	Encephalopathy/leukodystrophy, telangectasias, microcephaly, height at –3.9 SD	No	2	2	No	Uncategorized Inherited Syndrome
H69	M	15.7	Persistent mild bicytopenia since age 2 yo BMF on routine FBC	Sibling with AML Abnormal caryotype: t(1;16), add(3p) and 5q-	No	2	2	No	Uncategorized Inherited Syndrome
H73	F	6.5	Dyserythropoiesis since birth	Chronic recurrent multifocal osteomyelitis, height at –1SD	No	2	2	No	Uncategorized Inherited Syndrome (resembling Majeed syndrome, LPIN2 not mutated)
H75	F	20.7	Bicytopenia at age 12 BMF on routine FBC	'Facial dysmorphism', short stature, increased HbF, history of false positive chromosomal breakage test on PBL	No	2	n/a	n/a	Uncategorized Inherited Syndrome
H78	F	8	New onset epistaxis, gingivorrhagia	IUDD, severe thrombocytopenia since age 7 yo, initially treated as ITP with no response. Duplication of left renal system, increased Hemoglobin F, short fingers.	No	2	2	No	Uncategorized Inherited Syndrome
H80	M	16.3	Thrombocytopenia at age 13 yo BMF on routine FBC	Microphtalmia, hypospadia, small ears, plagiocephaly, narrow palpebral fissures, retrognathia, long toes, hypotonic soft palate, brother with polidactyly	No	2	n/a	n/a	Uncategorized Inheriited (microdel 22q11.2, not DiGeorge phenotype)
H81	F	14.2	Incidental diagnosis on routine FBC	Thrombocytopenia and dysmegakaryopoiesis since 18 mo, stable until age 14 yo when progressed to BMF with myelofibrosis. No skeletal malformations. Parents consanguineous.	No	2	2	No	Uncategorized Inherited Syndrome
H82	F	41.6	Incidental diagnosis of macrocytic anemia and dyserythropoiesis rapidly evolving into BMF	Facial dysmorphy, short stature, 'café-au-lait' spots	No	2	2	No	Uncategorized Inherited Syndrome
H85	F	3.7	Palor and fatigue	Macrocytosis, increased HbF, dyserythropoiesis on bone marrow aspirate/biopsy, atypical response to cyclosporin (initially given for a diagnosis of IAA), 2 'café-au-lait' spots	No	2	2	No	Uncategorized Inherited Syndrome/IAA
H86	F	0.6	Anemia at birth rapidly evolving into BMF	Severity and precocity of BMF, normal physical exam	No	2	2	No	Uncategorized Inherited Syndrome
H87	F	3	Incidental diagnosis of anemia with developmental delay at age 1yo	Hypotelorism, microphtalmia, 'facial dysmorphy', thumb malformation, unilateral vesicoureteral reflux, short stature (-2 SD).	No	2	2	No	Diamond-Blackfan

BMF indicates bone marrow failure; FBC: full blood counts; IAA: idiopathic aplastic anemia; M: masculin; F: feminin; PE: physical exam; PBL: peripheral blood lymphocytes; MMC: mitomycin C; FANCD2: immunoblot for detection of the FANCD2-L isoform ('2'-bands: normal pattern with both the short and long isoforms;'1'-band: abnormal FA pattern); n/a: not available; w/u: work-up; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; HbF: hemoglobin F; IgM: immunoglobulin M; IUDD: intrauterine developmental delay; ITP: immune thrombocytopenia purpura; AML: acute myeloid leukemia; URTI: upper respiratory tract infection; SD: standard deviation; AFP: alpha-fetoprotein.[§]: indicates hematopoietic reversion.

Online Supplementary Table S2. Patients with BMF and isolated positive clinical findings in history of physical exam (n=18).

					Biological Diagnosis				
					PBL		Fibroblast		
Patients		Age (y)	BMF Presentation	Findings in History or PE	Increased Breaks	FANC D2	FANC D2	Hypersensitivity to MMC	Final Diagnoses
H02	M	18.3	Incidental diagnosis on routine work up	Low birth weight, genu varum "Peculiar" facies, height at –2.1 SD	No	2	2	No	Idiopathic aplastic anemia
H04	M	10.2	See Table 3	See Table 3	INC	2	1	Yes	Fanconi Anemia[§]
H12	M	27.6	Relapsed AA diagnosed on routine FBC follow up	AA post acute hepatitis A at age 8 yo, relapse refractory to ATG/CSA	No	2	2	No	Idiopathic aplastic anemia (history of HVA)
H17	M	8.3	Petechiae	"Peculiar" facies	No	2	2	No	Idiopathic aplastic anemia
H18	F	17.3	Incidental diagnosis on w/u for tooth extraction	Precocious puberty, symetrical clinodactyly, height at –1.8SD	No	2	2	No	Idiopathic aplastic anemia
H19	M	35.9	See Table 3	See Table 3	Yes	1	1	Yes	Fanconi Anemia
H28	F	20.6	Palor and fatigue	Family history of miscariages 2 café-au-lait spots	No	2	2	No	Idiopathic aplastic anemia
H31	M	15.1	Incidental diagnosis on routine follow up for behavioral eating disorder	1 café-au-lait spot, history of leukaemia in family, height at –1.7SD, previous false positive chromosomal breakage test on PBL	No	2	2	No	Idiopathic aplastic anemia
H40	M	7.4	Ecchymoses and fatigue	2 café-au-lait spots	No	2	2	No	Idiopathic aplastic anemia
H46	M	22.1	Petechiae	Thumb malformation	No	2	2	No	Idiopathic aplastic anemia
H48	M	50.8	See Table 3	See Table 3	INC	1	1	Yes	Fanconi Anemia
H54	M	10.7	New onset fatigue, hematomas	1 café-au-lait spot Previous false positive chromosomal breakage test on PBL	No	2	2	No	Idiopathic aplastic anemia
H56	F	10.5	Ecchymoses	Multiple cancers in family Vitilligo at age 8 yo	No	2	2	No	Idiopathic aplastic anemia
H61	M	26.2	See Table 3	See Table 3	Yes	1	1	Yes	Fanconi Anemia
H62	F	19.4	Incidental diagnosis after 6 mo history of weight loss	Consanguinity, increased A FP	No	2	2	No	Idiopathic aplastic anemia
H64	F	9.3	Ecchymoses and palor	Cardiac septal defect at birth (spontaneous resolution), mother with coagulation Factor II mutation and miscarriages	No	2	n/a	n/a	Idiopathic aplastic anemia
H71	F	6.9	Incidental diagnosis on routine follow up for mild neutropenia since age 4 yo	History of GH deficiency (height at –4SD)	No	2	2	No	Idiopathic aplastic anemia
H84	F	29.8	Massive epistaxis during late 3rd trimester of 4th pregnancy	Sickle cell trait, previous false positive chromosomal breakage test on PBL, no consanguinity	No	2	2	No	Idiopathic aplastic anemia

IAA indicates idiopathic aplastic anemia; BMF: bone marrow failure; M: masculin; F: feminin; PE: physical exam; PBL: peripheral blood lymphocytes; MMC: mitomycin C; FANCD2: immunoblot for detection of monoubiquitination of FANCD2 ('2'-bands: normal pattern; '1'-band: abnormal FA pattern); INC: inconclusive; n/a: not available; SD: standard deviation; HVA: hepatitis virus A; ATG: anti-thymocyte globulin; CSA: cyclosporine; AFP: alpha-fetoprotein; GH: growth hormone.[§]: indicates hematopoietic reversion.