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# Low-dose non-steroidal anti-inflammatory drugs: a promising approach for the treatment of symptomatic bone marrow failure in Ghosal hematodiaphyseal dysplasia

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*JB and FSdF designed the study, collected the patients and wrote the original version of the manuscript. FSdF, FS, RPdL, SV took care and enrolled the patients in the RIME database. VCD, JS, MD, LL were responsible for molecular data analysis and performed the genetic diagnosis. VM provided data about bone marrow biopsies and pictures from figure S1. All authors contributed to reviewing and editing the manuscript and approved the final version.*

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Ghosal hematodiaphyseal dysplasia (GHD) is a rare autosomal recessive disease, characterized by severe anemia and painful long-bone diaphyseal cortical endosteal hypertrophy.[1] Some forty cases have been reported, mostly in childhood. The disease results from biallelic deleterious variants in the *TBXAS1* gene, disrupting TXAS protein function, causing thromboxane A2 pathway blockage and arachidonic acid metabolite accumulation.[2,3] Standard care involves systemic corticosteroids, effectively alleviating hematopoietic and bone disorders. However, patients often require long-term corticosteroids, leading to iatrogenic complications.

Based on the thromboxane A2 pathway dysregulation, Brown et al.[4] reported the good efficacy for the first time of cyclo-oxygenase 1 (COX1) and 2 (COX2) inhibition with non-steroidal anti-inflammatory drugs (NSAIDs) in two patients. Based on a similar hypothesis, four other non-related patients with GHD were treated in France from June 2019 with low-dose NSAIDs.

The French bone-marrow failure observatory (study's ethic committee approval CLEA-2023-#312) was consulted to identify patients with biallelic pathogenic *TBXAS1* variants, who underwent low doses of aspirin or NSAID treatment.

During screening, four unrelated patients were identified among 1,857 patients included in the observatory. Patients and disease characteristics are detailed in Table 1. Our four patients are male, with no other medical history than GHD. Patients #1, #3 and #4 presented a severe transfusion-dependent anemia in early childhood. Patients #1 and #3 achieved spontaneous red blood cell (RBC) transfusion independence without treatment for over 20 years. Patient #4 had required a long-lasting steroid treatment, with partial response and occasional RBC transfusions. Patient #2 had no hematological issues before the age of 24.

In the months preceding treatment with NSAIDs, all patients had severe anemia (median 6.8 g/dL, range 5.6-8.0) and thrombocytopenia (median 85 $10^9$/L, range 67-110), with normal neutrophil count, except for Patient #4 (neutrophil count 0.7 $10^9$/L) and presented mild inflammation (median CRP 31 mg/L, range 12.8-65). Clinically, moderate obesity was reported in three of them (Patient #1, #2 and #3) and a hepatosplenomegaly only in Patient #4. All had increased cortical density with diaphyseal involvement on bone X-ray, with a history of associated long-bone pain without skeletal deformity. Bone marrow aspirations failed, and biopsies revealed hypoplasia of the three myeloid lineages with dysmyelopoietic features, and with oedema and fibrosis (Figure S1). Investigations to rule out a myeloid malignancy were normal and genetic analyses for classical inherited bone marrow failure (Table 1) reported only the *TBXAS1* variants. Genetic diagnosis occurred with a median time of 15.5 years (range 4-34) after the first symptomatic anemia.

Patients #3 and #4 had received high-dose steroids with a good response, but treatment was discontinued, due to relapse, after discontinuation and high-dose steroid requirement, respectively. Patient #1 had received hydrocortisone therapy at 100 mg per day with a weak response.

Before treatment with aspirin, Patients #1, #2 and #4 required monthly RBC transfusions for over a year, while Patient #3 was promptly treated with aspirin after the discontinuation of corticosteroids, due to worsening anemia, before requiring RBC transfusions. None of the patients required platelet transfusions.

The median age of patients at the start of treatment with NSAIDs was 26 years (range: 23-40 years), corresponding to median delay of 21 months (range: 1-48 months) from the first transfused anemia episode for Patient #2, or from the relapse of anemia for the others. Aspirin

was initiated at 75 mg per day, excepted for Patient #3, who received 3 g per day (rheumatological dosage for rapid relief of bone pain).

All patients experienced a rapid hematological response (Figure 1), with the hemoglobin level reaching >100 g/L without transfusion at a median of 43 days (range 10-121), and were transfusion-independent at one month with bone pain resolution. Their platelet count exceeded 100 $10^9$/L in less than four months. For Patient #4, the neutrophil count improved to over 1.0 $10^9$/L. The biological inflammatory syndrome initially resolved in all patients, concomitantly of hematological parameter improvement.

During follow-up, Patient #2 suddenly stopped the treatment for two months, resulting in a relapse of anemia and inflammatory syndrome. A new complete hematological response occurred one month after resumption of treatment, indicating an aspirin-dependence profile.

Patient #4 also relapsed on aspirin 75 mg/day, with the reappearance of an inflammatory syndrome followed by anemia. As suggested by Brown et al.,[4] patients may have had different residual TBXAS1 enzyme activity, and in some cases required a higher aspirin dose. Therefore, a dose of 500 mg per day was introduced, with the current follow-up too short to assess response. Patient #4 was the only patient with a chronic disease evolution since childhood, associated with the emergence of steroid resistance and clinical hepatosplenomegaly, probably related to extensive bone marrow fibrosis. Another consideration, if improvement stalls despite dose escalation, is that the prolonged illness duration has severely impacted the bone marrow, hindering effective hematopoiesis through treatment.

With a median follow-up of 15.5 months (range: 9.5-52 months), Patients #1, #2 and #3 sustained a complete hematological response (on aspirin 75 mg daily for Patient #1 and #2, and on a reduced dose of 2 g per month for Patient #3, due to persistent remission).

Considering spontaneous hematological improvement during childhood in our Patients #1 and #3, we looked for a correlation between the phenotype and *TBXAS1* genotype. Analysis of our patients and genetically confirmed cases in the literature[3–10] (Table S1) revealed three phenotypes, as summarized in Table 2.

Firstly, a group of hematological asymptomatic carriers, or with at worse moderate anemia, with no history of RBC transfusion reported (Group 1, n=5). They were diagnosed at a median age of 16 years, during familial screening of a symptomatic relative. Although they all had abnormal bone X-rays consistent with GHD, no bone symptoms were reported. Interestingly, most were female (80%).

The second profile (Group 2, n=4) comprised patients with childhood-onset of severe anemia, necessitating RBC transfusions (discovered at a median of 25 months), who achieved a spontaneously hematological improvement after a mean time of 3.5 years (range 1-6.5), allowing RBC transfusions to be stopped. Three patients relapsed after a prolonged asymptomatic hematological period (12.5 to 28 years), presenting severe transfused anemia with clinical and radiological bone manifestations and a biological inflammatory syndrome.

The last profile (Group 3, n=14) included patients with early severe and persistent/long lasting transfusion-dependent anemia (median age at onset of two years), associated with thrombocytopenia and leukopenia for most cases. They all had radiological bone involvement, with half of them experiencing bone pain. Twelve patients were treated with high-dose corticoids as first-line therapy (the other two received NSAIDs as first-line), with a

good hematological response in each. However, only 25% of these patients were able to stop steroids without relapse (data available for eight patients with a short follow-up).

No genotype/phenotype correlations were identified (Supplemental Table S2). Inter- and intra-familial heterogeneity suggest unknown factors affecting phenotype, as possibly the female sex, more frequent in asymptomatic patients (Group 1: 80%, versus Groups 2+3: 20%). In Groups 2 and 3, the appearance of anemia coincided with a biological inflammatory syndrome, which may reflect disease activity. Otherwise, external factors, such as infections, might also trigger the disease worsening by generating inflammation and stimulating the arachidonic acid pathway, exacerbating metabolic problems caused by *TBXAS1* mutations, and contributing to clinical heterogeneity. However, grouping patients is challenging, due to the heterogeneity of the population and the reported data, but also due to the lack of information on follow-up for asymptomatic patients and the impact of treatment on disease spontaneous outcome.

Our four GHD patients, treated with low-dose aspirin, confirm the treatment's efficacy with three sustained hematological responses. Our last patient, despite an initial response, relapsed and is currently being treated with a higher dose. Hypotheses to explain the loss of response were non-compliance, drug interaction and a more severe enzymatic defect. Considering the treatment's excellent tolerability, especially its lower infection risk compared with corticosteroids, low-dose NSAIDs appear promising. However, data on the efficacy of NSAIDs in correcting radiological bone lesions are lacking, unlike steroid treatment, for which some pediatric studies have reported improvements.

Our review of the literature highlights the clinical heterogeneity of the disease, including the possibility of long-lasting spontaneous hematological improvement in childhood, which has been rarely reported so far. In most of these patients, anemia required RBC transfusions over a prolonged period, supporting a treatment by low-dose NSAIDs as soon as transfusions are required. No genotypic or clinical predictive factors were identified to predict a spontaneous improvement, which would have helped us to discuss the discontinuation of treatment in some patients. For others, such as Patient #2, who relapsed quickly after treatment was discontinued, suggesting NSAIDs dependency, lifelong treatment would seem necessary.

Lastly, our study highlights the importance of considering GHD in adults, as well as in children presenting with severe anemia and thrombocytopenia, especially in the case of abnormally tough bones, independently of myelofibrosis or radiological findings. Given the low toxicity of aspirin, *TBXAS1* mutation should be added to inherited bone marrow failure (IBMF) screening, especially if transplantation is considered. Unlike other IBMFs, no evolution to myeloid malignancy has been reported. While most reported cases involved children without long-term follow-up, five patients (four from our study) provided reassuring follow-up data into their fourth decade.

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| | Patient #1[A] | Patient #2[A] | Patient #3[A] | Patient #4[A] |
|---|---|---|---|---|
| **PATIENT CHARACTERISTICS** | | | | |
| **Age (years) at start of NSAIDs** | 40 | 28 | 24 | 23 |
| **Aspirin dose** | 75 mg/d | 75 mg/d | 3 g/d | 75 mg/d |
| **Sex** | Male | Male | Male | Male |
| **Origin** | Tunisian | Tunisian | Tunisian | Tunisian |
| **Family history of GHD** | No | No | One brother | No |
| **Age at first disease manifestations** | 6y | 24y | 25m | 14m |
| **Spontaneous remission and duration** | Yes, 28 years | No | Yes, 20 years | No |
| **History of high-dose steroid treatment** | No | No | Yes, steroid dependency | Yes, loss of efficacy |
| **Age (years) at molecular diagnosis** | 40 | 28 | 23 | 12 |
| ***TBXAS1* mutations (bi-allelic)** | c.1417G>T, p.Gly473Trp | c.1417G>T, p.Gly473Trp | c.245T>C, p.Leu82Pro | c.1417G>T, p.Gly473Trp |
| **SPECIALIZED HEMATOLOGICAL INVESTIGATIONS** | | | | |
| **Blood analysis** | | | | |
| **Blood smear** | No dysplasia | Rare dacrocytes | No dysplasia | No dysplasia |
| ***PNH clone*** | Negative | Negative | Negative | Small clone: 2% |
| **Bone marrow aspiration** | | | | |
| **Cytology examination** | Diluted, non-contributory | Diluted, non-contributory | Diluted, non-contributory | Diluted, non-contributory |
| **Karyotype** | Failed | Normal (but limited to seven cells) | Normal | Normal |
| **Chromosomal breakage analysis** | Normal | Normal | Not performed | Normal |
| **IBMF panel screening*** | No additional mutation | No additional mutation | Not performed** | No additional mutation |
| **Bone marrow biopsy** | | | | |
| **Richness** | Very severe hypoplasia | Severe hypoplasia, richness: 20% | Very severe hypoplasia, richness: grade 1 | Severe hypoplasia, richness: grade 1-2 |
| **Medullary fibrosis***** | Grade 1 with interstitial oedema | Grade 1 with interstitial oedema | Grade 3 + Osteosclerosis | Grade 3 |
| **Affected hematological lineages** | Severe damage to all three lines | Severe damage to all three lines | Severe damage to all three lines | Severe damage to all three lines |
| **Dysplasia** | Signs of dysmega-karyopoiesis and dyserythro-poiesis | Signs of dysmega-karyopoiesis and dyserythro-poiesis | Signs of dysmega-karyopoiesis and dyserythro-poiesis | No dysplastic features described |
| **CLINICAL AND BIOLOGICAL PARAMETERS BEFORE TREATMENT WITH NSAIDs** | | | | |
| **Hemoglobin level (g/L)** | 90 | 55 | 80 | 56 |
| **Numbers of PRBCs over the last six months before the start of NSAIDs treatment** | 14 | 6 | 0 | 12 |
| **Reticulocyte count** | N/A (55.4 G/L five months ago) | 50 | N/A | 55 |
| **Platelet count** | 52 | 68 | 109 | 95 |
| **Neutrophil count** | 1.8 | 2.3 | 2.4 | 0.7 |
| **CRP (mg/dL)** | 31 | 50 | 12.8 | 100 |

| | | | | |
|---|---|---|---|---|
| **Radiological bone involvement[B] / Bone pain** | +/+ | +/+ | +/+ | +/+ |
| **TREATMENT RESPONSE** | | | | |
| **Time to hemoglobin level response (days)[C]** | 21 | 121 | 38 | 48 |
| **Time to platelet level response (days)[D]** | 65 | 121 | N/A | 76 |
| **Persistent transfusion independency** | Yes | Yes | Yes | No |
| **Persistent hematological response [E] at six months** | Yes | Short relapse post-aspirin cessation, with a second complete response obtained one month after reintroduction. | Yes | Loss of response with RBC transfusion required under treatment at 75mg. |
| **Follow-up (months)** | 17 | 14 | 52 | 9.5 |
| **Hematological response at end of follow-up** | Yes | Yes | Yes | No |

**Table 1: Patient characteristics and main outcomes.**

$\mathcal{A}$: No family relationship between the patients could be established on examination, NSAIDs: non-steroidal anti-inflammatory drugs, y: years, m: months, d: days. GHD: Ghosal hematodiaphyseal dysplasia, PNH clone: paroxysmal nocturnal hemoglobinuria, CRP: C-reactive protein, PRBCs: packed red blood cells. $\mathcal{B}$: Bone abnormality was defined as typical long bone X-rays revealing an increased cortical density with diaphyseal involvement, often associated with bone pain. $\mathcal{C}$: Hemoglobin level response is defined as a hemoglobin level ≥100g/L without transfusion in the last month. $\mathcal{D}$: Platelet level response is defined as a platelet level ≥100 $10^9$/L without transfusion in the last month. $\mathcal{E}$: Hematological response is defined as an association of hemoglobin level and platelet level responses, with no bone pain related to the disease. It is counted as persistent if no relapse episode has been recorded since it was obtained.

* IBMF (Innate Bone-marrow Failure) panel includes *ARID2, ASXL1, ASXL2, ATRX, BCOR, BCORL1, BRAF, BRCA1, BRCA2, BRCC3, CALR, CBL, CEBPA, CHEK2, CLPB, CREBBP, CSF3R, CSNK1A1, CTCF, CUX1, DDX41, DNMT3A, ELANE, EP300, ERCC6L2, ETNK1, ETV6, EZH2, FLT3, GATA2, HRAS, IDH1, IDH2, IKZF5, IRF1, JAK2, JAK3, KDM5A, KDM6A, KIT, KMT2A/MLL, KMT2D/MLL2, KRAS, LUC7L2, MBD4, MECOM, MPL, MPO, MYC, NF1, NPM1, NRAS, PDS5B, PHF6, PPM1D, PRPF8, PTEN, PTPN11, RAD21, RIT1, RUNX1, SAMD9, SAMD9L, SBDS, SETBP1, SF1, SF3B1, SMC1A, SMC3, SRP72, SRSF2, STAG2, TET2, TERC, TERT, TP53, U2AF1, U2AF2, WT1, ZNF687, ZRSR2* and *TBX1S1*. *TBXAS1* is currently included in the IBMF panel, but it has been studied specifically in our patients.

** For Patient #3, in the context of a confirmed GHD in his brother, a targeted investigation with confirmation of the *TBXAS1* mutation and a restricted panel to screen for myeloid hemopathy were carried out.

*** The bone marrow biopsies from patients #1 and #2 underwent reassessment by two specialized hematopathologists who reported that the fibrosis observed is unusual with notably an interstitial oedema.

| | All | Group 1: Asymptomatic without history of RBC transfusion | Group 2: Spontaneous hematological remission history Data at first episode / (data at relapse) | Group 3: Symptomatic without history of spontaneous remission |
|---|---|---|---|---|
| **n** | 23 | 5 | 4 (relapse: 3) | 14 |
| **Median age* (range)** | 6y (5m-34y) | 16y (6-24y) | 4y (18m-6y) | 2y (5m-34y) |
| **Sex** | 16M/7F | 1M/4F | 3M/1F (2M/1F) | 12M/2F |
| **Bone pain** | 4/10 | 0/2 | 1/1 (3/3**) | 4/8 |
| **Pathological bone X-ray** | 23/23 | 5/5 | 2/2 (2/3)*** | 14/14 |
| **Anemia** | 20/23 | 2/5 (moderate) | 4/4 (3/3) | 14/14 |
| **RBC transfusion** | 13/19 | 0/5 | 4/4 (3/3) | 8/9 |
| **Thrombopenia** | 15/22 | 0/5 | 3/4 (3/3) | 12/13 |
| **Leucopenia** | 6/20 | 0/5 | 0/2 (0/3) | 5/13 |
| **IS** | 10/17 | 0/5 | 0/1 (3/3) | 10/14 |

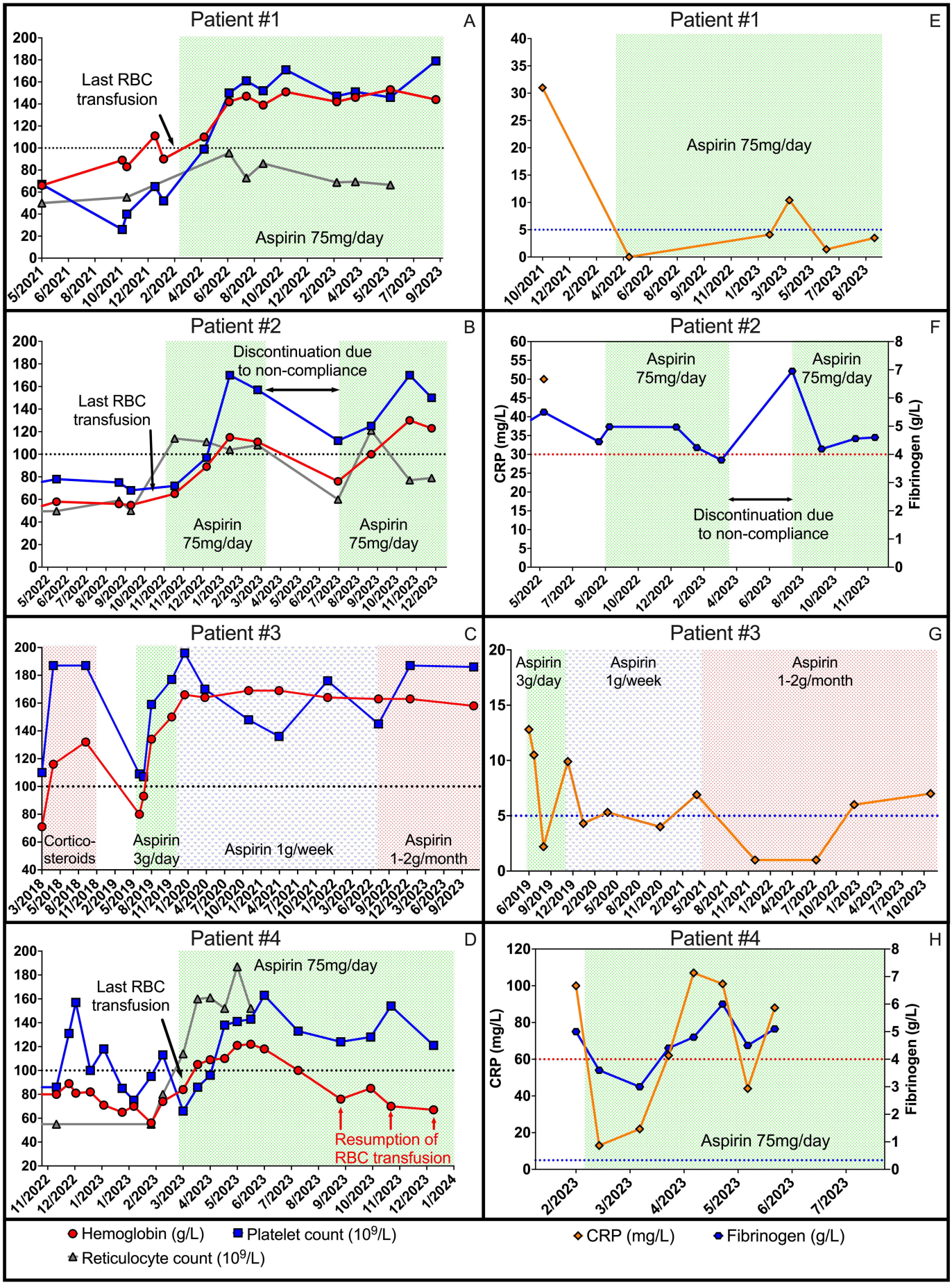
## Table 2: Sub-group phenotype description.

Asymptomatic: no hematological disorders, n: number of patients, m: month, y: years, M: male, F: female, RBC transfusion: red blood cell transfusion, Age: age or first symptoms (or diagnosis if age of first symptoms is not known), IS: positive inflammatory syndrome, *: Age at first symptoms or at diagnosis if asymptomatic,**: Not reported for three patients at first symptoms but all of them had bone pain at relapses, ***: two patients have a pathological bone radiography at diagnosis, the two other patients have a pathological bone radiography at relapse (no data for first episode), all patients have a history of pathological bone radiography typical of GHD during their lifetime.

## Figure 1: Graphs of the main hematological and inflammatory biological parameters during treatment.



Figures A, B, C and D represent hematological results and figures E, F, G and H represent inflammatory results. CRP: C-reactive protein. Standard for CRP positive determination set at >5mg/L represented by dashed red line (----) and for fibrinogen at > 4g/L represented by the blue line (----). The shadowed background represents the evolution of results under aspirin treatment. The green color indicates the initial aspirin dose, while the change in color corresponds to a change in dose. For Patient #4, inflammatory results were missing at relapse and at the end of follow-up.

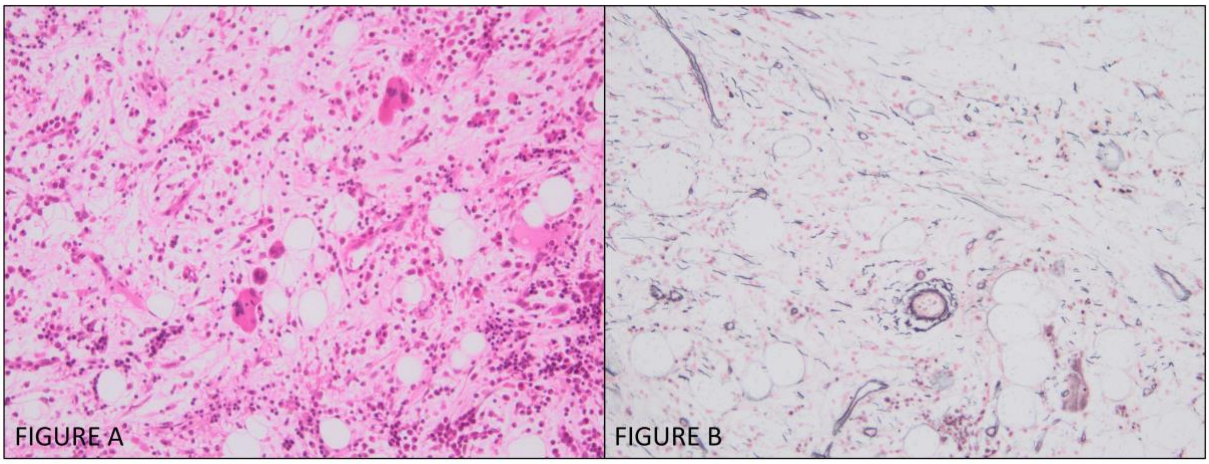

Patient #1
A
Last RBC transfusion
Aspirin 75mg/day
Patient #1
E
Aspirin 75mg/day
Patient #2
B
Last RBC transfusion
Discontinuation due to non-compliance
Aspirin 75mg/day
Aspirin 75mg/day
Patient #2
F
CRP (mg/L)
Fibrinogen (g/L)
Aspirin 75mg/day
Aspirin 75mg/day
Discontinuation due to non-compliance
Patient #3
C
Cortico-steroids
Aspirin 3g/day
Aspirin 1g/week
Aspirin 1-2g/month
Patient #3
G
Aspirin 3g/day
Aspirin 1g/week
Aspirin 1-2g/month
Patient #4
D
Last RBC transfusion
Aspirin 75mg/day
Resumption of RBC transfusion
Patient #4
H
CRP (mg/L)
Fibrinogen (g/L)
Aspirin 75mg/day
Hemoglobin (g/L)
Platelet count (10^9/L)
Reticulocyte count (10^9/L)
CRP (mg/L)
Fibrinogen (g/L)

## Table S1: List of genetically documented GHD cases reported and their clinical features (see excel file)

$\mathcal{A}$: siblings, $\mathcal{B}$: twins, *: but the X-ray could not be reviewed in the center, m: months, y: years, M: male, F: female, Hb: hemoglobin level, RBC: red blood cell transfusion, IS: positive inflammatory syndrome, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NSAIDs: non-steroidal anti-inflammatory drugs, NA: non-applicable, AE: adverse event, NOS: not otherwise specified, Hom: homozygous, HetC: composite heterozygous mutation. #: The latest HGVS nomenclature was used. The transcript used is NM_001061.7, corresponding to the updated RefSeq one and retained by MANE select. It is linked to the protein NP_001052.3 where the 473 amino acid is a Glycin and the 474 is an Alanine. All the variants described in the literature were update for harmonize purposes.

## Table S2: TBXAS1 mutation comparison in GHD subgroups (see excel file)

n: number of patients, Hom: homozygous, HetC: composite heterozygous mutation. The latest HGVS nomenclature was used. The transcript used is NM_001061.7, corresponding to the updated RefSeq one and retained by MANE select. It is linked to the protein NP_001052.3 where the 473 amino acid is a Glycin and the 474 is an Alanine. All the variants described in the literature were update for harmonize purposes.




## Figure S1: Bone marrow biopsy of Patient #2

Figure A: hypocellular bone marrow (20%) with dysmegakaryopoiesis and dyserythropoiesis associated with pronounced interstitial oedema (HES x 200).
Figure B: slight densification of the reticulin framework (WHO grade 1) (Reticulin staining x 200).
The fibrosis associated with interstitial edema, which is unusual, is characteristic of these biopsies.