Refractory idiopathic pure red cell aplasia complicated by immune thrombocytopenia successfully treated with subcutaneous alemtuzumab

To the Editor: Only rare case reports of patients with pure red cell aplasia (PRCA) responding to alemtuzumab exist; however, most are secondary PRCA with only one being idiopathic [1]. We report a man with refractory idiopathic PRCA complicated by ITP, successfully treated with subcutaneous alemtuzumab.

In Jan 2007, a 69-year-old man presented with idiopathic PRCA, refractory to treatments from 1993 to 2001 with anti-thymocyte globulin, prednisone, cyclosporine, cyclophosphamide, and rituximab 375 mg/m^2 weekly $\times$ 8. He required 2–3 units of red blood cells monthly with mean Hb 5–7 g/dl prior to transfusion. In 2005, he developed asymptomatic ITP with platelet count (PLT) 60–80 $\times$ 10^9/l, which dropped to 20–40 $\times$ 10^9/l over 2 years. Bone marrow biopsy and aspirate in Feb 2007 showed absence of erythroid precursors, presence of normal myeloid cells, and megakaryocytes. He was then treated with subcutaneous alemtuzumab with baseline Hb 6.8 g/dl, PLT 22 $\times$ 10^9/l, and WBC 5.3 $\times$ 10^9/l. He received test doses of 3 mg on Day 1, and 10 mg on Day 4. WBC then dropped to 1.2 $\times$ 10^9/l, which necessitated G-CSF 480 mcg daily until it normalized. On Day 18, he received alemtuzumab 30 mg, followed by pegfilgrastim 6 mg the next day for anticipated neutropenia. This was then repeated every 2 weeks on Days 32, 46, 60, 74, and 88. The cumulative dose was 193 mg. PLT rose to 83 $\times$ 10^9/l on Day 31, reached 180 $\times$ 10^9/l on Day 46, then stayed in the normal range. Hb increased to 8.6 g/dl on Day 88, reached 11.7 g/dl on Day 153, and then remained in the 11–12 g/dl range (Fig. 1). He became transfusion independent since Day 46. Bone marrow biopsy and aspiration on Day 153 showed presence of erythroid precursors, and decreased myeloid cells. At the most recent visit, he remained transfusion independent with Hb 12.1 g/dl, PLT 161 $\times$ 10^9/l, and WBC 3.5 $\times$ 10^9/l. No major toxicity of alemtuzumab was noted other than asymptomatic leukopenia.

Alemtuzumab has been shown to be effective in treating PRCA (idiopathic or secondary) and ITP, although the experience for these conditions is very limited [1–3]. It appears to be more effective than rituximab in treating PRCA, underlying the importance of T-cell modulation in PRCA [3]. Previous reports of PRCA involved intravenous use of alemtuzumab and did not document any patient with both idiopathic PRCA and ITP effectively treated with alemtuzumab. Our patient was, however, successfully treated with subcutaneous alemtuzumab despite 14 years since diagnosis. Subcutaneous alemtuzumab is an effective treatment option for refractory PRCA with durable remission, helps patients to become transfusion independent, and should be studied as a treatment for ITP. The dose and schedule of alemtuzumab for PRCA are not known due to limited anecdotal experience; however, a total dose of less than 200 mg can provide durable remission. Patients should be monitored closely, take prophylactic antibiotics, and receive granulocytes growth factor support as needed.

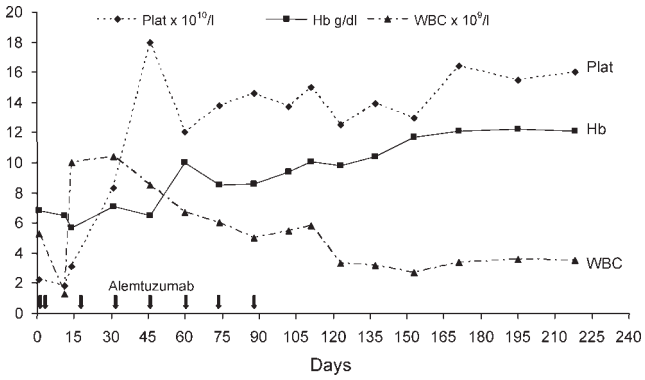

Figure 1. Platelet count (Plat), hemoglobin (Hb), and white blood cell count (WBC) during and after alemtuzumab therapy for a patient with refractory idiopathic pure red cell aplasia complicated by immune thrombocytopenia. Alemtuzumab was given subcutaneously at 3 mg on Day 1, and 10 mg on Day 4, then 30 mg on Day 18, 32, 46, 60, 74, and 88.

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A new TMHA-DHPLC assay for the rapid mutation screening of JAK2 exon 14 in myeloproliferative disorders

To the Editor: V617F mutation in exon 14 of JAK2 gene has been reported in more than 90% of patients with polycythemia vera (PV) and in near 50% of patients with essential thrombocythemia (ET) or idiopathic myelofibrosis. Molecular screening for the presence of V617F is becoming part of the current diagnostic process for these disorders and thus rapid and reliable methods are required. Moreover, given the recent description of two novel nucleotide exchanges next to V617F [1,2], it would be preferable to have an assay able to detect all mutations of potential patogenetic relevance in exon 14.

In a recent study [3], a method based on temperature modulated heteroduplex analysis (TMHA) through DHPLC is used. This method is unfortunately not sufficiently sensitive for V617F detection in a clinical setting. The poor sensitivity of TMHA-DHPLC method is related to the heterogeneous melting profile of the amplicons. The melting temperature of the region surrounding V617F mismatch is very different from that at the ends of the generated amplicons. Partially denaturing conditions of the region of interest are obtained at a very high temperature, causing destabilization and denaturation of the whole fragment (Fig. 1a).

To retain the advantages offered by the DHPLC technology, including its capability to potentially detect all exon 14 mutations, we devised a very fast and high-throughput modified TMHA-DHPLC assay adding a short stretch of nucleotides with a typical GC sequence to the forward primer (GC-clamp). Differently from the amplicon without GC-clamp, the new predicted melting curve was uniform for the entire target sequence (Fig. 1b,d). The addition of the clamp generated a region with a higher temperature compared with the target amplicon (Fig. 1d). Forward primer 5′-*cgcccgccgccgccc*tgcatctttattatgg-cagagaga-3′ and reverse primer 5′-cactgacacctagctgtgatcc-3′ was used and amplifications were performed under standard conditions. The chosen oven temperature was the highest at which the target sequence was predicted to be $\approx$ 90% double helix (Fig. 1c). As wild-type control, we used DNA from a subject lacking any exon 14 polymorphism. After standard heteroduplex creation, partially denaturating DHPLC screening was done in 3 min run. To evaluate the reliability of the GC-clamp TMHA-DHPLC in clinical practice, we

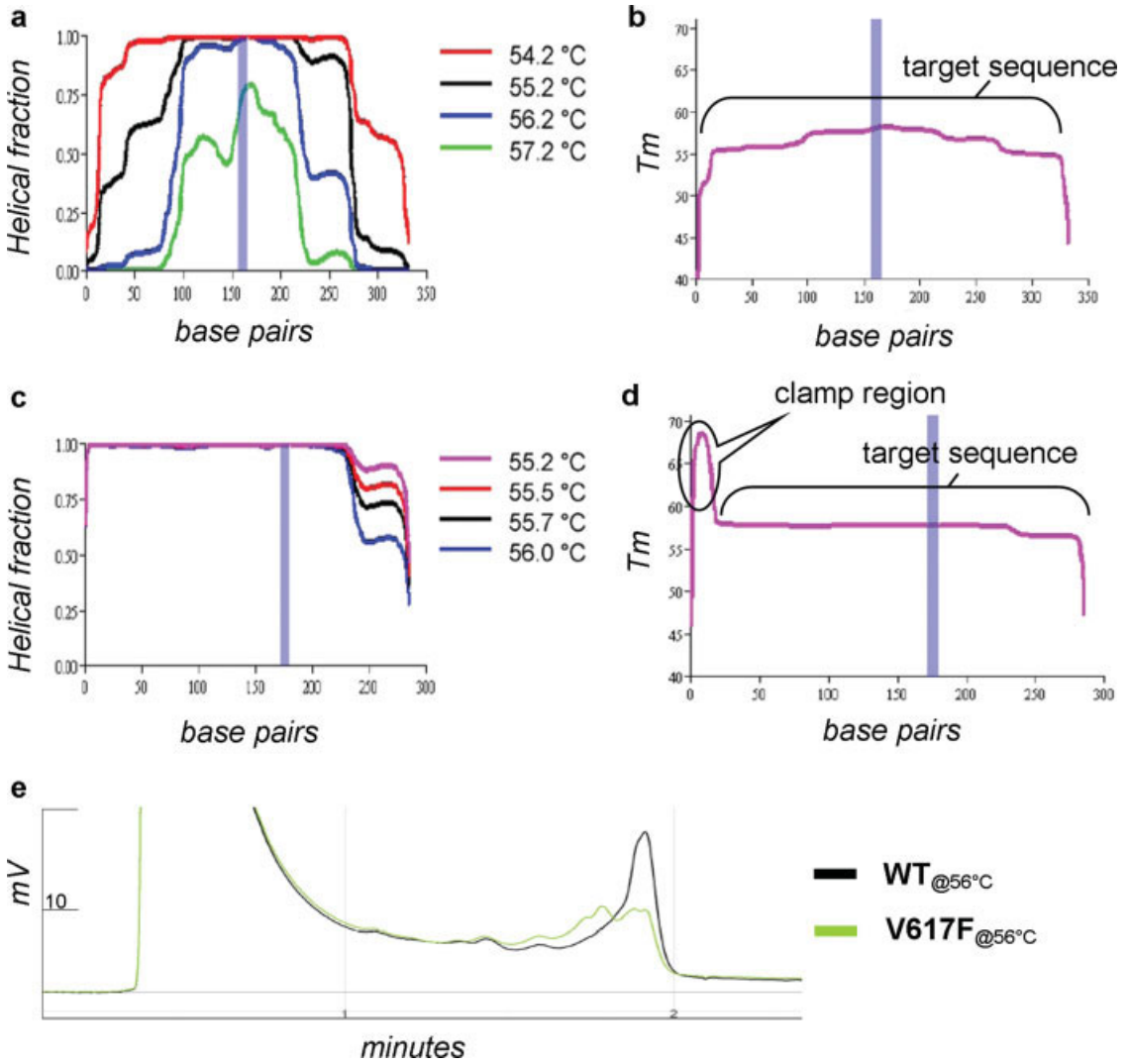

Figure 1. (a) Denaturing trends at different theoretical temperatures of the original amplicon containing JAK2 exon 14. The nucleotide region surrounding the V617F mutation was highlighted. Base pair position was plotted versus helical fraction ratio (0.00 value for 100% single stranded; 1.00 value for 100% double stranded). (b) Amplicon melting profile obtained under the original conditions without the inclusion of the 15-bases GC-clamp. The nucleotide region surrounding the V617F mutation was highlighted. Base pair was plotted versus the melting temperature (T_m, °C). The target sequence region is put in evidence. (c) Denaturing trends of the clamped amplicon containing JAK2 exon 14 at different temperatures. The nucleotide region surrounding the V617F mutation was highlighted. Base pair position was plotted versus helical fraction ratio (0.00 value for 100% single stranded; 1.00 value for 100% double stranded). (d) Amplicon melting profile with inclusion of a 15-bases GC-clamp on the 5′ amplification primer. Amplicon melting profile is uniform along the target sequence. The nucleotide region surrounding the V617F mutation was highlighted. The target sequence and the clamped regions were put in evidence. Base pair was plotted versus the melting temperature (T_m, °C). (e) DHPLC chromatogram revealing the presence of the V617F heteroduplex (green line) and the wild-type homoduplex control (black line). Retention time (minutes) was plotted versus the absorbance intensity (mV). Run was performed at 56°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

tested 148 PV and 176 ET patients with the new method in parallel with allele-specific PCR followed by amplification refractory mutation system PCR (AS/ARMS-PCR). In addition, 20 V617F heterozygous positive samples from PV and ET patients were also tested using standard TMHA-DHPLC. The presence of AS/ARMS-PCR V617F positive patients was confirmed in all cases by using GC-clamp TMHA-DHPLC by the distinct appearance of abnormal chromatographic profiles (Fig. 1e). On the contrary, standard TMHA-DHPLC was unable to detect mutated allele in 20 positive controls, confirming its insensitivity. Serial dilutions of a mixture containing the amplification product of a PV patient homozygous for JAK2 V617F and a wild-type control were tested. The JAK2 V617F mutation was clearly detected in presence of 1 mutated allele every 12 normal alleles.

With this new GC-clamp, TMHA-DHPLC assay laborious sample preparation and costly labeling procedures are avoided. This method appears reliable, high-throughput, and sensitive for the detection of allelic variants involving JAK2 exon 14 in peripheral blood of patients with myeloprolipherative diseases.

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Correlation of capillary and venous absolute neutrophil counts in adult hematological patients and normal controls

To the Editor: Absolute neutrophil counts (ANC) are being used to define neutropenia or agranulocytosis. ANC are essential for therapeutic strategies, e.g., antibiotic prophylaxis after aggressive chemotherapy. Capillary blood samples are easily obtained making results quickly available, but venous values are generally accepted as references.

We compared 447 pairs of capillary (fingerstick) and venous (cubital vein) ANC of 421 adult hematological patients (70%) and healthy subjects (30%) using a hematology analyzer (Advia 120, Bayer, Fernwald, Germany). Mean age of all subjects was 51 years, range 18–81 years; the ratio of male to female was 1:1. The most frequent diseases were malignant lymphoma (43%), multiple myeloma (17%), myeloproliferative diseases (14%), and acute leukemia (11%). Both blood samples were collected at the same time from each subject.

ANC were calculated on the basis of measured white blood cell counts and relative neutrophil counts. For statistical analyses, Student's *t*-test and Pearson's correlation coefficient (*r* value) were used; $P < 0.05$ was considered statistically significant.

No statistically significant differences were seen in the ANC, regardless whether capillary or venous sampling was done; capillary and venous ANC correlate very well. Likewise, no statistically significant differences were seen in capillary and venous ANC for patients with neutropenia (ANC $< 1.50 \times 10^9$/l) and agranulocytosis (ANC $< 0.50 \times 10^9$/l) (Table I). Importantly for routine clinical use, no local infectious complications were seen in patients with neutropenia or agranulocytosis after capillary fingerstick sampling. Also, no statistically significant differences between capillary and venous ANC were seen in comparison to both patients and healthy subjects ($P = 0.15$). Sensitivity to detect patients with neutropenia or agranulocytosis is high using capillary blood samples (95%). Furthermore, specificity is even higher (100%). The variation coefficient, defined as ratio of standard deviation to mean, of repeated capillary and venous measurements was 3.2% for capillary ANC and 2.4% for venous ANC.

In contrast to our results, in previously published studies capillary were found to be higher than venous ANC. For adults, data are lacking so far, because the cohort size up to $n = 40$ is not sufficient [1]. Furthermore, data for adult hematological patients are not available. In children, much higher capillary than venous ANC were found (17.2%; $n = 9$, aged 3 months to 14 years) in comparison to young adults (12.6%; $n = 24$, aged 20–22 years) and older adults (8.2%; $n = 40$, aged 22–62 years) [1–3]. Thus, it seems that there is an age-dependant tendency for higher capillary ANC that decreases with older age. Our different results may be explained by the fact that we have included a large cohort size and ~60% of subjects were above 50 years, most likely representing the age cohort of hematological patients.

Capillary ANC may be preferable in patients with poor or difficult peripheral access, especially because only small blood samples are used.

In conclusion, capillary and venous ANC correlate very well in adults. The capillary approach provides simple and reliable ANC in patients and normal subjects, and allows to detect true-positive and true-negative adult patients with neutropenia or agranulocytosis.

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Complications of β-thalassemia intermedia: A 12-year Lebanese experience

To the Editor: Thalassemia is an inherited disease that affects α- or β-chain molecules of hemoglobin [1,2]. The Middle East has one of the highest rates of incidence worldwide, and the Lebanese population specifically has 3% carrier prevalence with approximately one-third of the patients suffering from thalassemia intermedia (TI).

By definition, TI includes a wide clinical spectrum as follows: mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7 and 10 g/dl. These patients require only occasional blood transfusions, if any; patients with more severe TI generally present between the ages of 2 and 6 years, and although they are able to survive without regular transfusion therapy, their growth and development can be retarded.

The purpose of this study is to shed light on the complications for the Lebanese TI population. The TI patients are being followed up at the Chronic

TABLE I. Comparison of Capillary and Venous Absolute Neutrophil Counts (ANC)

	Capillary ANC ($\times 10^9$/l)[a]	Venous ANC ($\times 10^9$/l)[a]	Δ value ($\times 10^9$/l)	*r* value	*P* value
ANC (total, $n = 447$)	4.21 ± 3.85 (0.02–51.83)	4.28 ± 3.63 (0.02–41.61)	−0.07 (−1.0%)	0.98	0.05
Neutropenia ($n = 43$)[b]	0.66 ± 0.50 (0.02–1.71)	0.63 ± 0.48 (0.02–1.44)	+0.03 (+5.5%)	0.98	0.07
Agranulocytosis ($n = 19$)[c]	0.18 ± 0.18 (0.02–0.51)	0.16 ± 0.15 (0.02–0.46)	+0.02 (+6.7%)	0.97	0.15

[a]Mean, standard deviation, and range are indicated.
[b]ANC $< 1.50 \times 10^9$/l.
[c]ANC $< 0.50 \times 10^9$/l.
+ and −, capillary value is higher or lower, respectively, when compared with venous value; Δ value, capillary/venous difference.

TABLE I. Complications of TI Among 92 Patients

Complication	Number[a]	Prevalence of population
Congestive heart failure	1/92	1.1
Pulmonary hypertension (defined with TR > 30 mm Hg)	13/41[b]	31.7
Hypogonadism	10/92	10.9
Hypothyroidism	9/92	9.8
Diabetes mellitus	2/92	2.2
Extramedullary hematopoiesis	18/92	19.6
Thrombotic event	26/92	28.2
Leg ulcers	18/92	19.6
Hepatitis C	6/92	6.5
Splenectomy[c]	87/109	79.8

[a] The total number of complications exceeds the above listed number of patients with complications, since many patients have >1 complication.
[b] Only 41 TI patients had echocardiographic data available.
[c] Splenectomy is not considered a complication, yet it affects the overall survival of patients.

Care Center in Hazmieh, Lebanon. TI patients were selected according to the inclusion criteria of having received a transfusion after 2 years of age without regular transfusion dependency. Frequencies, Kaplan Meier plots, cross-tabs, and comparison of means were done using SPSS 13.0.

The overall analysis population consisted of 92 patients out of a total of 109 (51.1% females). All patients were born between 1970 and 2004. Average serum ferritin for patients without complications was lower than those with complications (911 ± 771 vs. 1347 ± 764; $P = 0.007$). In the survival analysis, the most recent birth cohorts (after 1994) had a more extended complication free period ($P = 0.009$) without any complications reported (Table I). Forty-four patients were born before 1983, and 31 patients were born between 1984 and 1993. There is significant difference in the incidence of complications, with a far worse disease progression for those born between 1984 and 1993 ($P = 0.003$). Furthermore, echocardiographic analysis of 41 patients revealed that thirteen (31.7%) patients suffered from pulmonary hypertension [3]. Known TI complications such as thrombosis, leg ulcers, and extramedullary hematopoiesis were present with the percentages of 28.2, 19.6, and 19.6%, respectively. The other complications were endocrinologic, with hypogonadism affecting 10.9% of patients ($n = 10$) and hypothyroidism affecting 9.8% ($n = 9$). Of the 109 patients whose charts were reviewed, 79.8% were splenectomized. After cross-matching each complication with splenectomy separately for any possible relationship, all splenectomized patients were found to develop hypothyroidism as a complication ($P = 0.049$). In addition, 9% ($n = 10$) of the patients are receiving irregular transfusions and chelation therapy (use chemical name, not Desferal).

Pulmonary hypertension is the most common complication among TI Lebanese patients (31.7%), followed by thrombotic events, leg ulcers, extramedullary hematopoiesis, endocrinologic dysfunction (hypogonadism and hypothyroidism), and infections. The prevalence of complications seems to differ when compared with the data reported from Italy [2]. We believe that magnetic resonance imaging-based iron overload evaluation of TI patients plays a major role in decreasing the incidence of complications [4].

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Bone marrow fibrosis and gelatinous atrophy associated with acute Epstein–Barr virus infection

To the Editor: The clinical presentation of Epstein–Barr virus (EBV) infection can vary widely [1]. The development of myelofibrosis in the context of EBV in adults has not been previously reported. A 21-year-old woman presented with high fever (103.8°F), confusion, and anorexia. Initial laboratory work revealed WBC 2.5 × 10^9/L (84% neutrophils, 10% lymphocytes, 1% monocytes, and 5% bands), hemoglobin 5.6 g/dL, platelet count 79 × 10^9/L, serum iron 66 mcg/dL, ferritin >2,000 ng/dL, total iron binding capacity 243 mcg/dL, lactate dehydrogenase 1,737 U/L, haptoglobin <6 mg/dL, reticulocyte count 1.4%, ALT 49 U/L, AST 200 U/L, total bilirubin 1.4 g/dL, and alkaline phosphatase 50 U/L. Coagulation studies were normal except for D-dimer >20 ng/mL and fibrin split products >20 μg/mL. Direct Coombs test was weakly positive for IgG but negative for C3, with a negative eluate. Peripheral blood smear revealed pancytopenia with a severe normocytic hypochromic anemia and occasional schistocytes. Daily plasma exchange was performed for five consecutive days, to no avail. The ADAMTS-13 activity returned at 37% (high risk of TTP <5%). Red blood cells transfusion increased the hemoglobin to 9.6 g/dL, but this rapidly decreased to 6.9 g/dL within 48 hr. A repeat Coombs test was negative with a reticulocyte count of 1.5%. Hepatitis B and C, and HIV testing were negative. Extensive rheumatic work-up was negative except for antinuclear antibodies (titer, 1:640). A bone marrow biopsy was hypocellular (40%) and the aspirate failed to demonstrate dysplasia, hemophagocytosis, malignancy, or acid-fast bacilli microorganisms. Scattered areas of gelatinous atrophy and diffuse reticulin fibrosis consistent with Grade 2 myelofibrosis [2] were demonstrated (see Fig. 1). Bacterial, fungal, and acid-fast bacilli cultures in bone marrow, as well as serum viral titers for parvovirus B-19 IgG and IgM and cytomegalovirus IgG and IgM were negative. However, EBV viral capside antigen IgG and IgM were 3.4 and 3.5, respectively (normal, <1.10). Further serologic testing confirmed acute EBV infection with EBV nuclear antigen Elisa Value IgG of 5.00 (normal, <1.10) and early antigen D Elisa Value IgG of 5.07 (normal, <1.00). After 5 days on valacyclovir, the patient became afebrile and was discharged with WBC 1.8 × 10^9/L, hemoglobin 10.3 g/dL, and platelet count 210 × 10^9/L.

While primary myelofibrosis is typically associated with chronic myeloproliferative disorders, most cases of myelofibrosis are secondary (Table I). In adult patients, myelofibrosis is exceedingly rare during the course of EBV infection in the absence of hemophagocytic syndrome (HPS) [3,4]. No cases of EBV-associated myelofibrosis in adults without evidence of HPS had been previously reported. A high EBV titer along with the presence of bone marrow hypocellularity and diffuse reticulin fibrosis and gelatinous transformation were deemed responsible for the bone marrow failure. The immediate institution of gancyclovir therapy resulted in swift resolution of the symptoms and remarkable improvement of the peripheral blood counts. Albeit a posttreatment bone marrow biopsy to ascertain whether the clinical improvement was paralleled by resolution of the marrow fibrosis and gelatinous transformation could not be obtained, this case highlights the therapeutic potential of gancyclovir in the management of acute EBV infection with bone marrow failure.

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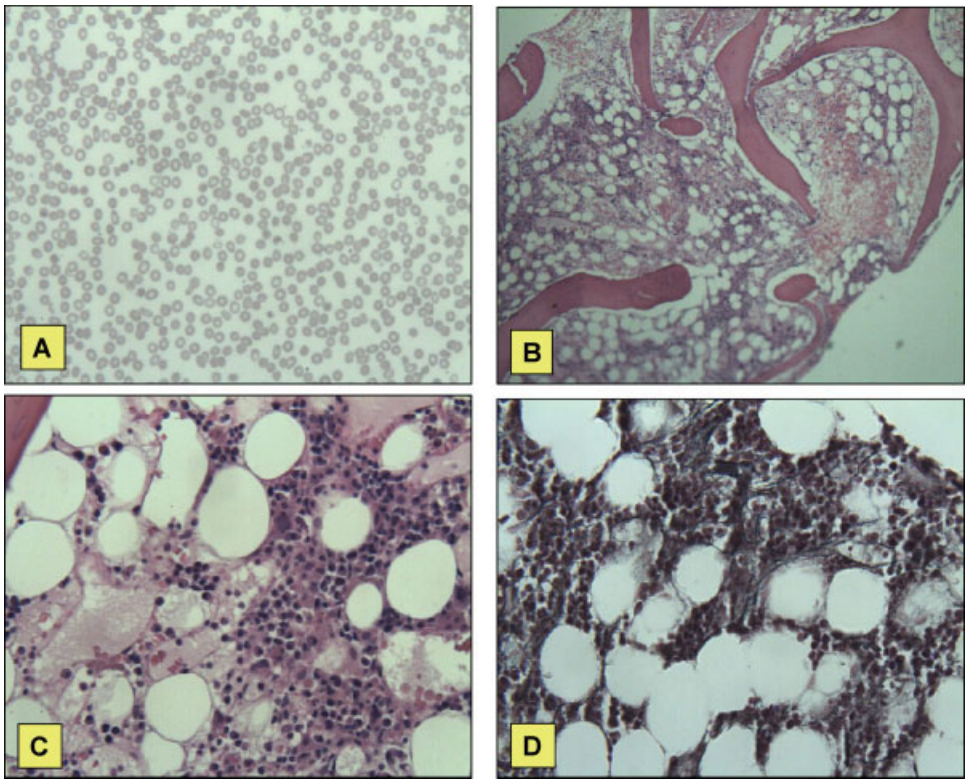

Figure 1. (A) Peripheral blood smear demonstrated hypochromic anemia with slight polychromasia. Platelets were normal in morphology but decreased in number. (B) Bone marrow biopsy specimen showing marked hypocellularity (40%), no evidence of granulomas or malignant cells. (C) There were scattered focal areas of gelatinous atrophy characterized by faintly staining eosinophilic material (hematoxylin–eosin stain). (D) Reticulin stain showed the presence of diffuse increase in reticulin fibers with occasional dense strands and many intersections, consistent with Grade 2 myelofibrosis. Original magnification: ×40 (B) and ×100 (A, C, and D). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I. Primary and Secondary Causes of Myelofibrosis

Primary or idiopathic	Myelofibrosis with myeloid metaplasia
Secondary	*Malignant*
	AML-M7
	CML
	ALL
	NHL
	Hodgkin disease
	Non-malignant
	Langerhans histiocytosis
	Hemophagocytic lymphohistiocytosis
	Infection
	Tuberculosis
	Histoplasmosis
	EBV
	Visceral leishmaniasis
	Renal osteodistrophy
	Vitamin D deficiency
	SLE
	Osteopetrosis
	Hyperparathyroidism
	Gaucher disease
	Radiation
	Gray platelet syndrome
	Pernicious anemia

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