

**LETTERS AND CORRESPONDENCE**

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**Recurrent Skin Reaction Secondary to Darbepoetin Alfa for Two Months in a Patient With Chronic Lymphocytic Leukemia**

*To the Editor:* A 74-year-old man diagnosed with chronic lymphocytic leukemia was started on darbepoetin alfa (Aranesp) at a dose of 1.5 µg/kg subcutaneously once every 2 weeks for treatment of anemia. However, after the third injection, he developed an orofacial angioedema, difficulty in swallowing, and generalized erythema and swelling, more severe on the face, neck, and arms. Blood workup revealed stable hemoglobin. Darbepoetin was discontinued and oral dexamethasone at 8 mg was started and tapered over 2 weeks. Symptoms subsided within a few hours; however, they recurred 1 week later. Dexamethasone was restarted at a dose of 4 mg for 2 more weeks, in addition to antihistamines. Immediate response was noted again, but symptoms recurred 1 week later. He received methylprednisolone intravenously at a dose of 125 mg for 6 hr over 3 days and then was discharged on oral prednisone 40 mg tapered over 2 weeks. No recurrence of symptoms was reported since then.

Darbepoetin alfa is a glycoprotein analogue of recombinant human erythropoietin (rHuEPO) [1]. It is made by the substitution of five amino acids in rHuEPO allowing for two additional oligosaccharide attachments in darbepoetin alfa [1]. These two chains increase the number of sialic acid residues within the molecule, thus increasing the in vivo biological activity and prolonging the half life ( $t_{1/2}$ ) by about three-fold compared with rHuEPO [1].

Skin reactions to rHuEPO include pruritis, wheals at the site of injections, anaphylaxis, generalized eczema, and orofacial angioedema. Although the manufacturer's US prescribing information mentioned that skin rash and pruritis occurred in 7% of patients taking darbepoetin alfa, only a few cases are reported in the literature [2]. One report mentioned urticaria and wheals at the sites of previous subcutaneous injections of epoetin. These reactions improved shortly after intravenous methylprednisolone [3]. In another report, generalized urticaria, pruritis, and orofacial edema developed after the third dose of Aranesp. The rash improved after 1 week and was attributed to polysorbate 80 excipient of Aranesp [4]. Change to polysorbate-free Aranesp did not illicit any reaction. The Aranesp given to our patient, however, is polysorbate-free and has human serum albumin as an excipient. To our knowledge, this is the first report of recurrent darbepoetin alfa-related hypersensitivity reactions persisting for 2 months despite discontinuation of

the medication, and despite adequate treatment with antihistamines and intermittent corticosteroids.

The etiology of the skin reaction in this patient is not clear. Since darbepoetin alfa has a different amino acid sequence from the endogenous erythropoietin, it might be immunogenic [2]. However, this immunogenicity is thought to be minimal due to the two additional N-linked carbohydrate chains shielding on the five dissimilar amino acids [2]. Actually, there are no reports of erythropoietin antibodies induced by darbepoetin. Regardless of the etiology, skin reactions secondary to darbepoetin alfa do occur and can be severe and prolonged due to the long half life of the drug. If they occur, we recommend discontinuing the drug and administering corticosteroids and antihistamines for 4–8 weeks to avoid anaphylaxis.

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**Treatment of Anemia in Myelodysplastic Syndrome With Darbepoetin and Granulocyte Colony Stimulating Factor**

*To the Editor:* Anemia in patients with myelodysplastic syndrome (MDS) can be improved by treatment with hematopoietic growth factors. Erythropoietin (EPO) alone has an overall response rate of 20% [1] and together with granulocyte colony stimulating factor (G-CSF) becomes more effective with an erythroid response rate of around 40% [2]. Darbepoetin, a modified form of EPO with a longer half-life, has been shown to be effective in correcting anemia in a significant proportion of MDS patients [3]. Synergy between darbepoetin and G-CSF has not been shown. We report the clinical course of a patient with MDS, who received darbepoetin and G-CSF combination (Fig. 1).

A 77-year-old male diagnosed with intermediate risk MDS (RAEB-I) had WBC 2,400/mm<sup>3</sup>, Hgb 9.7 g/dL, and platelets 106,000/mm<sup>3</sup>. Cytogenetics studies

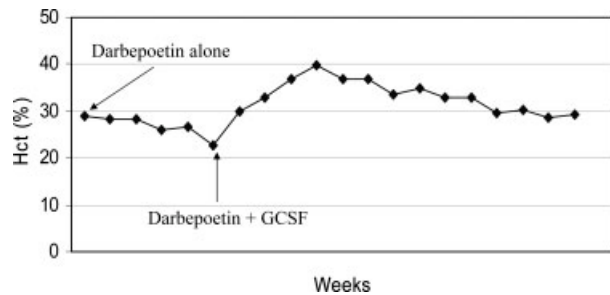


**Fig. 1. Erythrocyte response with combination of darbepoetin and G-CSF.**

showed a normal male karyotype. He was started on Procrit 20,000 U weekly, titrated up to 40,000 U weekly. This led to an increase in the Hgb to 12 g/dL. For convenience purposes, weekly Procrit was switched onto Aranesp (Darbepoetin) 100 mcg for 2 weeks. An initial drop in the Hgb to 11 g/dL required the Aranesp dose to be increased to 200 mcg for 2 weeks with resultant stabilization between 10 and 11 g/dL. Seven months later, Hgb dropped down to 9 g/dL and Aranesp was increased to 300 mcg for 2 weeks. This resulted in Hgb increase to 10 g/dL, which remained stable for the next 7 months. Hgb then dropped to 8.3 g/dL, though WBC and platelet count remained stable. The Aranesp dose was now increased to 300 mcg per week keeping Hgb stable between 9 and 10 g/dL for few months till the patient became transfusion dependent. He also progressively became neutropenic with ANC <500 and thrombocytopenic with platelets <50,000. At this point, he was started on G-CSF 480 mcg three times weekly along with darbepoetin 300 mcg weekly. This resulted in a dramatic improvement in the Hgb, WBC, and platelets. He continues to remain transfusion independent after 8 months of combination treatment maintaining Hgb between 10 and 11 g/dL.

Supportive care remains the mainstay of therapy in MDS and frequently includes hematopoietic growth factors, such as EPO, G-CSF, and GM-CSF [4]. Studies have shown a better erythrocyte response for the combination of EPO with G-CSF suggesting an in-vivo synergy. To our knowledge, there has been only one publication looking at the darbepoetin and pegfilgrastim combination and its effect on blood counts in a patient with MDS [5]. We report a patient with intermediate risk MDS who showed a significant erythroid response to darbepoetin plus G-CSF.

In other settings, combined EPO and G-CSF had either no effect on the platelet count or had a negative effect causing thrombocytopenia [2]. However, this patient in addition to having a major erythrocyte and neutrophil response also had an improvement in platelet count.

The course of this patient suggests that darbepoetin in combination with G-CSF improves anemia and neutropenia in patients with MDS who do not respond to darbepoetin alone. It also suggests that in-vivo synergy may exist between these two drugs for the production of red cells in MDS.

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## Successful Control of Severe Postoperative Bleeding With Recombinant Factor VIIa in a Case of Refractory Idiopathic Thrombocytopenic Purpura

*To the Editor:* Thrombocytopenia is one of the various “off-label” uses of activated recombinant factor VII (rFVIIa); efficacy of this hemostatic agent for the treatment of critical thrombocytopenia-associated bleeding has been reported [1–3].

There are no published data on the use of rFVIIa in patients with refractory idiopathic thrombocytopenic purpura (ITP) suffering from life-threatening bleeding.

Our patient was a 78-year-old man diagnosed with ITP in 2002, with a stable platelet count ( $40\text{--}60 \times 10^9/\text{L}$ ) without any specific treatment. In December 2005, a diagnosis of severe achalasia was made requiring surgery; platelet count had decreased at the time ( $10 \times 10^9/\text{L}$ ), and prednisolone treatment (1 mg/kg/24 hr intravenously) was started. Four weeks later, there was no platelet count recovery and preoperative intravenous immunoglobulins (1 g/kg for 2 days) were infused unsuccessfully. Platelet concentrates (1 U/10 kg) were administered and a platelet count of  $45 \times 10^9/\text{L}$  was recorded just at the time of surgery. Severe postoperative bleeding occurred in spite of repeated platelet transfusions and seven red blood cell (RBC) units were administered in the 12 hr following surgery. rFVIIa at a standard dose (90  $\mu\text{g}/\text{kg}$ ) was given at 0 and 2 hr with platelet concentrates and alone every 4 hr thereafter during the first 24 hr; subsequently, dose intervals were increased to 6 hourly for further 24 hr.  $\epsilon$ -Aminocaproic acid (4 g i.v. qds) was prescribed. Bleeding was stopped and no further RBC concentrates were transfused; bleeding did not recur postoperatively despite persistently extreme thrombocytopenia ( $<10 \times 10^9/\text{L}$ ).

From its approval, the number of clinical applications of rFVIIa has experienced a steady growth with severe bleeding due to thrombocytopenia being one of them; however, limited data on this use has been reported [1,3,4]. Kristensen et al. [1] reported their experience with rFVIIa in a heterogeneous group of 74 severely or moderately thrombocytopenic subjects; bleeding time was shortened in roughly half of cases, and clinical benefit achieved in all eight patients presenting with clinically significant bleeding. Bleeding time reductions were more consistent when platelet counts were  $>20 \times 10^9/\text{L}$ .

ITP as a cause of life-threatening hemorrhage is infrequent. A correlation between the degree of thrombocytopenia and clinical efficacy of rFVIIa has not been reported; consequently, there is no evidence to suggest that concomitant platelet transfusion is necessary. Nonetheless the activated platelet surface acts as a template on which rFVIIa can mediate thrombin generation at pharmacologic doses by a tissue factor-independent mechanism [5]. This was the theoretical basis for the initial infusion of platelet concentrates along with rFVIIa.

rFVIIa might be of use alone or in combination with platelet support in severely thrombocytopenic refractory ITP patients before major surgery or to stop severe postoperative bleeding. Data coming from properly designed trials would be necessary in order to find out the optimal dose, dose intervals, correlation between platelet count and efficacy of rFVIIa and need or convenience of simultaneous platelet concentrate infusion in this particular “off-label” clin-

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ical setting. Until these are available rFVIIa should only be used in the most extreme circumstances and in no way with the aim of sorting out potential surgical trouble.

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## A Novel t(4;11)(q21;q23) MLL-AF4 Fusion Transcript in Infant Leukemia

*To the Editor:* Chromosomal translocations involving *MLL* gene on 11q23 are detected in several types of leukemia [1]. One particular translocation, t(4;11)(q21;q23), occurs with high frequency (50–70%) in infant acute lymphoblastic leukemia (ALL). This translocation results in the fusion of *MLL* gene with *AF4* gene located at chromosomal band 4q21. The breakpoint on *MLL* gene occurs in a 6.5 kb region between exons 8 and 12. The breakpoint on *AF4* gene is larger (~40 kb) and involves a region between exons 3 and 7. Different *MLL-AF4* fusion transcripts have been detected depending on inclusion of exons within the breakpoint regions. The frequency of fusion transcripts detected varies between infant and non-infant ALL. Approximately 55% of infant *MLL-AF4* fusion transcripts include exon 11 of *MLL* and exon 4 of *AF4* [2].

Here we report an 11-month-old boy who presented with peripheral count of  $>400 \times 10^9/L$  consisting mostly of blasts. Immunophenotyping of the blasts showed B-lineage (positive for surface CD19 and cytoplasmic CD79a and negative for cytoplasmic CD3 and myeloperoxidase). The blasts were CD10 negative and expressed the myeloid marker CD15. Reverse transcription PCR analysis for t(4;11) using previously described primers [2] showed the presence of an unexpectedly smaller sized product. Sequence analysis of the PCR product revealed a previously undescribed *MLL-AF4* fusion transcript resulting from in-frame fusion of exon 9 of the *MLL* gene and exon 6 of the *AF4* gene. This sequence has been deposited in GenBank under accession number DQ451148.

*MLL-AF4* positive infant leukemia is generally associated with a poor outcome [3]. However, the prognostic significance of different *MLL-AF4* fusion transcripts has not been determined. Our patient achieved both morphological and molecular remission following the induction phase of chemotherapy. When compared to the most common *MLL-AF4* fusion transcript in infant ALL, our patient's transcript lacks exons 9 and 10 of *MLL* gene and exons 4 and 5 of *AF4* gene. The impact of combined deletion of these exons on the oncogenic potential of fusion gene and prognosis of infant ALL is unknown.

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## Pure Red Cell Aplasia Caused by Antibody to Erythropoietin Successfully Treated by Cyclosporine Administration

*To the Editor:* We previously reported the first Japanese case of pure red cell aplasia (PRCA) caused by antibody to erythropoietin (Epo) administered after erythropoietin- $\beta$  (epoetin  $\beta$ ) administration in a patient with anemia due to chronic renal failure [1]. The Epo neutralizing antibody level determined by radioimmunoprecipitation (RIP) was extremely high at the diagnosis of PRCA, 2.83  $\mu\text{g/ml}$  Epo-binding capacity, and those levels were serially determined thereafter (Fig. 1). This patient was treated with 200 mg/day of cyclosporine, along with hemodialysis. Although the antibody level decreased gradually, anemia persisted, and the patient remained red blood cell transfusion-dependent. After 2 years, when the neutralizing antibody titer decreased markedly to 1 in 1,000 (3.5 ng/ml Epo binding capacity minimally) but is still detectable [2], the patient was no longer dependent on red blood cell transfusion; maximally 9.8 g/

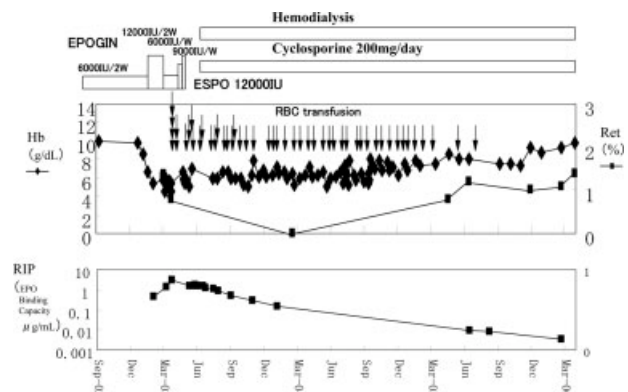


**Fig. 1. Clinical course.** EPOGIN: epoetin beta, Chugai, Tokyo, Japan; ESPO: epoetin alfa, Kirin, Tokyo, Japan; RIP: radioimmunoprecipitation.

dl of hemoglobin, which was above the criteria of 8 g/dl for independence from red blood cell transfusion [3].

The highest rate of epoetin responsiveness (89%) was noted among patients who had no detectable antierythropoietin antibodies at the time of epoetin readministration [3]. The hemoglobin level in the present patient has not yet reached the normal level, but is gradually increasing; however, the neutralizing antibody persists, although it is decreasing. Rechallenging of epoetin has not yet started because the patient is not willing to permit readministration of epoetin.

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## Late Relapse of Acute Promyelocytic Leukemia in a Patient With No Maintenance Therapy

*To the Editor:* Current standard therapy for acute promyelocytic leukemia (APL) includes all-trans retinoic acid (ATRA) and cytotoxic chemotherapy for remission induction and consolidation followed by ATRA or low-dose chemotherapy maintenance. The importance of maintenance therapy has been demonstrated in several trials with up to 70% improvement in long-term disease-free survival in ATRA maintenance group when compared to observation alone [1,2]. Here, we report a case of one patient who received ATRA induction and cytotoxic chemotherapy consolidation with no maintenance therapy and still experienced late relapse after 11-year prolonged remission. This patient responded to combined arsenic trioxide and ATRA induction therapy for the second remission.

A 52-year-old Haitian female was originally diagnosed with APL in October 1993. Laboratory studies at that time revealed the white blood cell count as  $1.2 \times 10^9/L$ , the hemoglobin as 9.1 g/dl, and the platelet count as  $12 \times 10^9/L$ . Bone marrow examination revealed diffuse infiltration by atypical promyelocytes (69%). Cytogenetic study revealed the t(15;17) (q22;q12–q21) chromosomal abnormality. The patient was enrolled into a phase III clinical trial and was randomly assigned to receive ATRA induction therapy (45 mg/m<sup>2</sup> per day). Complete remission (CR) was achieved on day 46 but the course was complicated by ATRA syndrome and intubation with ICU stay. The patient then received two cycles of consolidation therapy with cytarabine and daunorubicin and was randomly assigned to the observation arm of the study in March 1994. The patient was followed by a hematologist with regular blood tests and bone marrow exams and did well until February 2005 and after a disease-free survival of 11 years, she presented with ecchymosis and fatigue. Laboratory studies showed pancytopenia, and bone marrow exam and flow cytometric analysis were consistent with relapsed APL. The patient was started on induction therapy with both arsenic trioxide (0.15 mg/kg per day and 5 doses/week) and ATRA (45 mg/m<sup>2</sup> per day) and tolerated well with no evidence of ATRA syndrome or significant cardiac toxicity during

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the course. Remission was achieved on day 47. The patient then received two cycles of consolidation therapy and was put on maintenance therapy with ATRA. At the time of this study, the patient has remained in CR for more than 1 year.

Recurrence from APL mostly occurs within 2–3 years from CR achievement and late relapse is very rare beyond 7 years [1,3]. The case we report here not only represents the latest relapse from CR in the literature, but also shows us that APL is a heterogeneous disease with diverse clinical courses. It would be challenging to identify the prognostic markers in APL to guide the therapy regimen and the follow-up plan in individual patients.

Additive or synergistic activity between ATRA and arsenic trioxide when administered concomitantly or sequentially has been demonstrated by several groups [4,5]. The success of combined ATRA and arsenic trioxide induction regimen in our patient needs further investigation by large randomized trials.

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## Therapy-Related Chronic Myelomonocytic Leukemia With Unique Chromosomal Abnormalities: Monosomy 7 and t(12;17)(p13;q11.2)

*To the Editor:* Chronic myelomonocytic leukemia (CMML) is a progenitor stem-cell disorder characterized by peripheral blood monocytosis ( $> 1 \times 10^9/L$ ) in the context of myelodysplasia [1]. Cytogenetic abnormalities are frequently found, especially trisomy 8, monosomy 7, 20q deletion, and t(5;12)(q33;p13) [2]. We describe a case of CMML presenting with unique chromosomal abnormalities.

A 59-year-old white female patient presented in January 2003 with thrombocytopenia and macrocytic anemia. CBC revealed WBC  $11.9 \times 10^9/L$  (neutrophil 81%, band 5%, lymphocyte 7%, monocyte 6%, metamyelocyte 1%), hemoglobin 9.4 g/dL, MCV 111 fL, and platelet  $119 \times 10^9/L$ . In early 1990s, she was treated with cyclophosphamide for Wegener's granulomatosis (WG) for 12 months. She takes prednisone for WG. Physical examination was unremarkable except Cushingoid facies and pallor. Blood smear showed anisopoikilocytosis, tear drop forms, polychromasia, nucleated RBCs, basophilic stippling, metamyelocytes, pseudo-Pelger-Huet cells, and occasional giant platelets. Chemistry profile was normal except LDH 913 U/L (range 313–618 U/L), IgG 530 mg/dL (range 600–1,500 mg/dL), and IgM 32 mg/dL (range 50–300 mg/dL). Bone marrow was hypocellular (30%), with M:E ratio 2:1, trilineage dysplasia

without excess blasts, and adequate iron stores. Bone marrow cells yielded no dividing cells. A diagnosis of therapy-related refractory anemia (RA) was entertained. She was started on erythropoietin and oral iron, resulting in hemoglobin improvement. In July 2004, her platelet count declined to  $26 \times 10^9/L$  after decreasing prednisone dose for WG. Platelet count came up when prednisone dose was subsequently increased. Thrombocytopenia was felt to be partly immune-mediated. In December 2004, her CBC revealed WBC  $13.8 \times 10^9/L$  (neutrophil 71%, band 5%, lymphocyte 11%, monocyte 11%, metamyelocyte 1%, nucleated RBC 1%), hemoglobin 10.5 g/dL, and platelet  $15 \times 10^9/L$ . Bone marrow biopsy revealed hypercellularity (75%) and trilineage dysplasia (erythroid cells 67%, blast 2%, promyelocyte 3%, myelocyte 5%, metamyelocyte 7%, band and segment 6%, lymphocyte 2%, monocyte 8%). A diagnosis of CMML was established. Bone marrow cells karyotype revealed 45,XX, -7 [3], idem, t(12;17)(p13;q11.2) (17), (monosomy 7 in all 20 cells and 17 cells showed a further change, i.e., translocation between chromosomes 12p13 and 17q11.2). FISH analysis showed deletion of TEL gene on chromosome 12.

To our knowledge, this is the first case of therapy-related CMML with monosomy 7 and t(12;17)(p13;q11.2). This case also has notable features, (a) morphologic evolution from RA to CMML, (b) hypogammaglobulinemia, and (c) component of immune thrombocytopenia. Review of the Cancer Genome Anatomy Project database revealed 32 cases of hematologic malignancies associated with t(12;17); 16 cases of acute lymphoblastic leukemia, 13 cases of acute myeloid leukemia, 2 cases of acute biphenotypic leukemia, and 1 case of and peripheral B-cell neoplasm [3]. TEL gene was discovered at chromosome 12p13 as a fusion gene of platelet-derived growth factor- $\beta$  from a CMML patient [4]. In our case, TEL gene deletion might have contributed to leukemogenesis. Similar to our case, autoimmune phenomena have been described in CMML patients [5]. We propose that this case seems to be of value for the study of the significance of chromosomal abnormalities in CMML.

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## Oxidative Stress in Asymptomatic Subjects With Hereditary Hemochromatosis

*To the Editor:* Increased oxidative stress has been reported in hereditary hemochromatosis (HH) subjects and phlebotomy therapy appears to be an effective approach to attenuating it [1,2]. However, there is a paucity of data on oxidative stress status in HH subjects undergoing chronic phlebotomy therapy. To address this issue, during the National Heart, Lung, and Blood Institute sponsored clinical study *Heart Study of Hemochromatosis* [3], we measured oxidative stress-related biochemical markers in three asymptomatic age- and gender-matched groups: newly diagnosed HH subjects (Group A,  $n = 22$ ), HH subjects who had undergone at least six months of phlebotomy therapy (Group B,  $n = 21$ ), and control subjects lacking C282Y and H63D mutations in the HFE gene (Group C,  $n = 21$ ). All HH subjects were recruited from the community and documented to be homozygous for the C282Y HFE mutation and to have New York Heart Association functional Class I cardiac status [3]. Erythrocyte glutathione, erythrocyte superoxide dismutase, plasma lipid oxidation assayed as the sum of malondialdehyde and 4-hydroxy-2 alkenals, and plasma myeloperoxidase were measured as biomarkers of oxidative stress.

The mean duration of phlebotomy therapy in Group B subjects was  $59 \pm 71$  (data are mean  $\pm$  SD; range, 6-238) months. Surprisingly, Group B subjects demonstrated significant elevations in erythrocyte glutathione, plasma lipid peroxidation, and plasma myeloperoxidase levels when compared with controls (Table I). Abnormalities in oxidative stress markers in Group A subjects were limited to erythrocyte glutathione. Although the study population was small and measurements were limited to conventional biomarkers of oxidative stress, the results show significant elevations in oxidative stress levels in chronically treated HH subjects.

TABLE I. Oxidative Stress-Related Biomarkers in Hereditary Hemochromatosis and Control Subjects

| Variables                                | Hereditary hemochromatosis |                      | Controls<br>(Group C; $N = 21$ ) |
|------------------------------------------|----------------------------|----------------------|----------------------------------|
|                                          | (Group A; $N = 22$ )       | (Group B; $N = 21$ ) |                                  |
| Age (years)                              | 48 $\pm$ 11                | 51 $\pm$ 9           | 48 $\pm$ 8                       |
| Females (%)                              | 27                         | 33                   | 33                               |
| Ferritin ( $\mu$ g/L)                    | 1164 $\pm$ 886**           | 128 $\pm$ 262        | 98 $\pm$ 76                      |
| Transferrin saturation (%)               | 76 $\pm$ 19**              | 42 $\pm$ 21*         | 26 $\pm$ 10                      |
| Hemoglobin (g/dL)                        | 14.6 $\pm$ 1.6             | 14.2 $\pm$ 0.9       | 14.2 $\pm$ 1.1                   |
| Hematocrit (%)                           | 44.3 $\pm$ 4.5             | 42.1 $\pm$ 2.8       | 41.9 $\pm$ 3.6                   |
| Erythrocyte glutathione ( $\mu$ M/gHb)   | 6.7 $\pm$ 4.5*             | 8.3 $\pm$ 4.2*       | 3.6 $\pm$ 1.8                    |
| Erythrocyte superoxide dismutase (U/gHb) | 45.3 $\pm$ 9.6             | 48.9 $\pm$ 12.7      | 46.8 $\pm$ 12.7                  |
| Plasma lipid peroxidation ( $\mu$ M)     | 2.4 $\pm$ 1.5†             | 3.5 $\pm$ 2.0*       | 2.0 $\pm$ 1.2                    |
| Plasma myeloperoxidase (ng/mL)           | 26.7 $\pm$ 23              | 69.8 $\pm$ 123.8*    | 4.6 $\pm$ 4.7                    |

Group A, Newly diagnosed hereditary hemochromatosis (HH) subjects; Group B, Chronically treated HH subjects; Group C, Normal volunteers; gHb, gram of hemoglobin. Statistical analysis was performed by a Kruskal-Wallis test.

\* $P < 0.05$  vs. Group C and † $P < 0.05$  vs. Group B. Data are expressed as mean  $\pm$  SD.

In addition to these baseline evaluations, 21 Group A subjects underwent repeated analysis after completing the first six months of phlebotomy therapy (removal of 200–225 mg of iron every 1–4 weeks), during which there was a significant reduction in systemic iron burden (ferritin  $1209 \pm 881 \mu\text{g/L}$  vs.  $280 \pm 452 \mu\text{g/L}$ ,  $P < 0.01$ ; transferrin saturation  $77 \pm 18\%$  vs.  $50 \pm 27\%$ ,  $P < 0.01$ ). Oxidative stress markers significantly declined after this treatment (erythrocyte  $6.8 \pm 4.6 \mu\text{mole/gHb}$  vs.  $4.1 \pm 1.3 \mu\text{mole/gHb}$ ,  $P < 0.001$ ; plasma myeloperoxidase  $27.3 \pm 23.3 \text{ ng/ml}$  vs.  $14.3 \pm 6.2 \text{ ng/ml}$ ,  $P < 0.05$ ). These data suggest that initial, intensive phlebotomy therapy attenuates oxidative stress in HH subjects with iron overload [1,2].

Our results imply that oxidative stress may persist or rebound during the chronic maintenance phase of phlebotomy therapy in HH subjects. In contrast, initial, intensive iron depletion by phlebotomy attenuates oxidative stress in newly diagnosed subjects. These findings may be partly explained by the fact that the chronically treated patients were a very heterogeneous group, treated for a longer time and perhaps with less attention to consistent iron control than the newly diagnosed patients. Further investigation is warranted to confirm our preliminary observations on a larger scale.

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## Successful Splenectomy in Cancer-Associated TTP

*To the Editor:* Thrombotic thrombocytopenic purpura (TTP) is a rare complication of neoplastic disease with a poor outcome [1]. The poor prognosis of cancer-associated TTP (Ca-TTP) is largely a reflection of the relative ineffectiveness of therapeutic modalities used to treat the idiopathic form such as plasmapheresis and immunotherapy. In cases of refractory and relapsing idiopathic TTP, splenectomy has been used with promising results [2]. However, splenectomy has not been explored as a treatment option for refractory Ca-TTP. We report a case of a patient with TTP secondary to metastatic breast cancer who showed a complete response to splenectomy.

A 51-year-old female presented with a  $12 \text{ cm} \times 12 \text{ cm}$  invasive right-sided breast cancer. She received chemotherapy with four cycles of cyclophosphamide and doxorubicin, followed by radical mastectomy. Pathology revealed a  $9 \text{ cm} \times 9 \text{ cm}$ , ER-PR positive, and Her-2 negative breast cancer. Surgery was followed by four cycles of paclitaxel, local radiotherapy, and tamoxifen. Four years later, the patient relapsed with symptomatic bone disease that responded to docetaxel and vinorelbine. One year later, the patient presented with metastatic liver disease. She received a single dose of gemcitabine  $1000 \text{ mg/m}^2$  and docetaxel  $20 \text{ mg/m}^2$ . Hemoglobin was  $11.4 \text{ g/dL}$  and platelets were  $124 \times 10^9/\text{L}$ . One week later, a CBC showed a hemoglobin of  $8.4 \text{ g/dL}$ , WBC of  $2.4 \times 10^9/\text{L}$ , and a platelet count of  $15 \times 10^9/\text{L}$ . Reticulocyte count was 7%. Peripheral smear showed nucleated red cells, polychromasia, occasional myelocyte, and 1.6% schistocytes. PT and PTT were normal. D-dimer was  $> 4 \mu\text{g/mL}$ . Antiglobulin test was negative and serum haptoglobin  $< 6 \text{ mg/dL}$  (normal 36–225 mg/dL). Urea nitrogen and creatinine were normal. Other labs included bilirubin

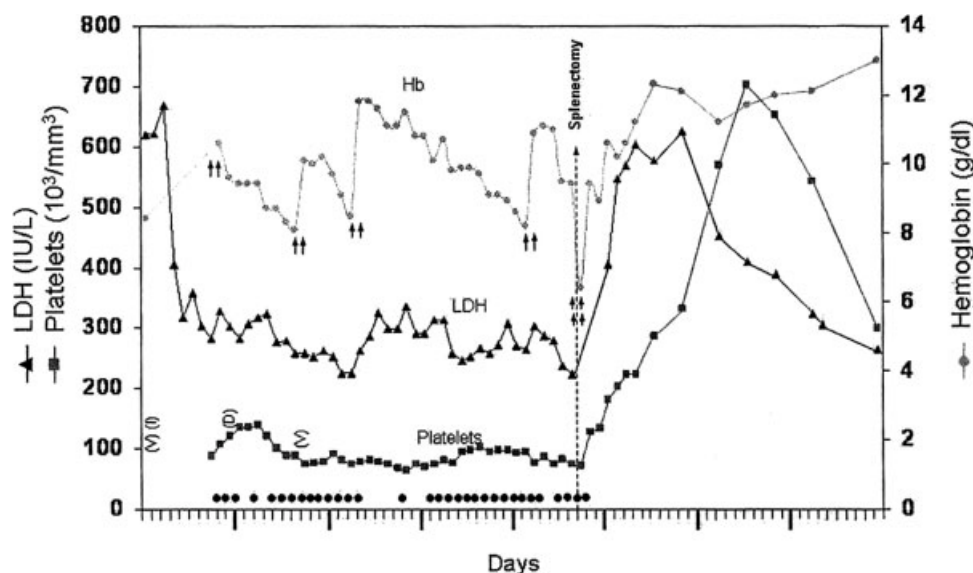


Fig. 1. Clinical course of the patient. (●) Plasma therapy, (††) packed cell transfusions, (†) intravenous immunoglobulin therapy, (V) vincristine, (D) docetaxel.

23.9  $\mu\text{mol/L}$  (normal 0–17.1  $\mu\text{mol/L}$ ), LDH 669 IU/L (normal 90–200 IU/L), alkaline phosphatase 304 IU/L (normal 30–130 IU/L), AST 183 IU/L (normal 0–41 IU/L), and ALT of 124 IU/L (normal 0–45 IU/L). ADAMTS13 activity was normal and no inhibitor was detected. CA 27.29 levels were 122 units (normal 0–40 units). Since the cumulative doses of gemcitabine and docetaxel administered were smaller than those reported in chemotherapy-associated TTP [3,4], a diagnosis of Ca-TTP was made. Plasmapheresis was initiated. The patient received two doses of vincristine ( $\text{mg/m}^2$ ) a week apart and a single dose of IVIG 400 mg/kg. She remained refractory to the therapy with plasmapheresis. Forty six days after her initial presentation, a splenectomy was performed.

Clinical course is summarized in Fig. 1.

Pathology of the spleen revealed adenocarcinoma. Six months postsplenectomy, CBC and LDH remain normal and no hematological support was needed. Her CA 27.29 levels have increased to 249 units.

This is the first reported case of refractory Ca-TTP successfully treated with splenectomy. Further experience is needed to establish the role of splenectomy in the management of Ca-TTP, but it should be considered as an option in refractory cases. Once hematologically stable, the patient can safely undergo treatment of their malignant disease with chemotherapy, which has been associated with longer survivals [5].

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## Rapid Determination of ADAMTS13 Activity Improves Clinical Decision-Making

*To the Editor:* Although thrombotic thrombocytopenic purpura (TTP) remains a clinical diagnosis, the rapid and reliable assessment of ADAMTS13 activity would be essential to clinicians evaluating patients with unexplained thrombocytopenia and microangiopathic findings. The finding of normal ADAMTS13 activity could help differentiate TTP from other thrombotic microangiopathies that can present similarly, but do not require plasma exchange (PE), minimizing the exposure to the potential risks of PE [1]. Our group has reported a novel assay to measure ADAMTS13 activity using surface enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectrometry that allows for the rapid and reliable determination of ADAMTS13 activity, giving clinicians real-time (< 4 hr) data to assist clinical decision making [2]. Here we report the clinical utility of this assay in helping to differentiate idiopathic TTP from a hypertensive crisis.

*Patient 1:* The first patient is a 38-year-old African American man with a history significant for hypertension who presented with complaints of epistaxis, headache, blurry vision, and hematuria. Physical exam was remarkable for a blood pressure of 225/152 mmHg. Laboratory studies showed severe thrombocytopenia of  $14 \times 10^9/\text{l}$  (range, 150–400  $\times 10^9/\text{l}$ ) and a hemoglobin of 10 g/dl. The serum creatinine was elevated at 3.5 mg/dl (range, 0.9–1.3 mg/dl) and the lactate dehydrogenase was elevated to 1053 U/l (range, 0–190 U/l). Evaluation of the peripheral smear revealed numerous schistocytes per high power field. Given the clinical suspicion for TTP, the patient underwent urgent PE. The following morning pretreatment ADAMTS13 activity was found to be > 60% by the SELDI TOF-based method. Given this data, PE was discontinued and aggressive blood pressure control continued with the gradual resolution of the laboratory abnormalities and symptoms.

*Patient 2:* The second patient is a 40-year-old African American who presented with complaints of shortness of breath, chest pain, numbness, and tingling of his lower extremities. Physical examination was notable for a blood pressure of 215/163 mmHg. Laboratory studies were significant for a platelet count of  $50 \times 10^9/\text{l}$  and hemoglobin of 10.7 g/dl. The serum creatinine was also elevated at 4.4 mg/dl (range, 0.9–1.3 mg/dl), and the lactate dehydrogenase was increased to 3042 U/l (range, 0–190 U/l). Numerous schistocytes were appreciated in the peripheral blood smear. Within 3 hr and prior to initiating PE therapy, ADAMTS13 activity was determined to be > 60% by the SELDI-TOF-based methodology. Based upon the clinical presentation and normal ADAMTS13 activity, PE therapy was withheld and the patient clinically improved with aggressive antihypertensive therapy.

Patients with a hypertensive crisis may exhibit clinical features that overlap with idiopathic TTP making a definitive diagnosis difficult [3,4]. More importantly, both conditions require urgent but significantly different therapeutic interventions. The availability of a rapid and reliable ADAMTS13 assay will be invaluable to clinicians in helping to establish the correct diagnosis and initiate the most appropriate therapy. The demonstration of normal ADAMTS13 activity in both reported cases provided the supportive data to justify withholding PE and minimize the potential risks associated with PE therapy.

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