Federation, where some specialists had advocated the DOTS strategy as a "cost-effective" panacea for rising tuberculosis rates[3] — without mention of the need to diagnose and treat already prevalent drug-resistant strains — a manyfold increase in multidrug-resistant tuberculosis has been observed.[4] In Belarus, more than 35% of new tuberculosis cases involve multidrug-resistant strains.[5] These trends are alarming and have undoubtedly been exacerbated by a serious omission in the DOTS strategy. A critical review of the intellectual roots of the current approach is an important first step in furthering a conversation about how to close a number of important gaps in the global struggle against tuberculosis.

Salmaan Keshavjee, M.D., Ph.D.
Paul E. Farmer, M.D., Ph.D.
Harvard Medical School
Boston, MA
salmaan_keshavjee@hms.harvard.edu

Since publication of their article, the authors report no further potential conflict of interest.

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ADAMTS13 Antibody Depletion by Bortezomib in Thrombotic Thrombocytopenic Purpura

TO THE EDITOR: Inhibitory autoantibodies against ADAMTS13, a metalloproteinase enzyme that cleaves von Willebrand factor, are associated with the majority of nonfamilial cases of thrombotic thrombocytopenic purpura (TTP). Therapeutic plasma exchange aims to remove autoantibodies while replenishing levels of ADAMTS13.[1] Adjunctive immunosuppression is often required and may include selective B-cell depletion with rituximab.[1,2] Here we report a case of acute TTP in which the disease was refractory to plasma exchange and immunosuppression. Subsequent treatment with the proteasome inhibitor bortezomib resulted in a rapid clinical response associated with in vivo depletion of inhibitory autoantibodies against ADAMTS13.

A 53-year-old woman presented with fever, headache, focal neurologic signs, and microangiopathic hemolysis without renal dysfunction or diarrhea. The ADAMTS13 activity was undetectable, with a level of ADAMTS13 autoantibodies of 3.2 Bethesda units (BU). Treatment was initiated with daily plasma exchange and prednisolone (at a dose of 1 mg per kilogram of body weight) (Fig. 1A). Antiplatelet agents were withheld owing to intermittent melena. Unfortunately, the patient's condition deteriorated despite increasing the plasma-exchange regimen to twice daily (8 liters per day) and the administration of pulsed methylprednisolone (total dose, 3 g, followed by continuous infusion of 120 mg per day).

On day 9, the patient was admitted to the intensive care unit with progressive neurologic impairment necessitating endotracheal intubation. Magnetic resonance imaging showed diffuse cerebral microhemorrhages and a 2-mm brain-stem infarct. Further immunosuppression, including cyclophosphamide (2.5 g total) and rituximab (375 mg per square meter of body-surface area weekly for 4 weeks), was administered. An infusion of *N*-acetylcysteine (2.5 g per day) was started on the basis of a report of efficacy in TTP-prone mice.[3] However, the patient remained dependent on plasma exchange without clinical improvement and with a persisting autoantibody titer of 2.2 BU on day 22. Splenectomy was considered but not performed because of refractory thrombocytopenia and the recent brain-stem infarct.

A bone marrow biopsy sample obtained on day 25 showed objective evidence of effective B-cell

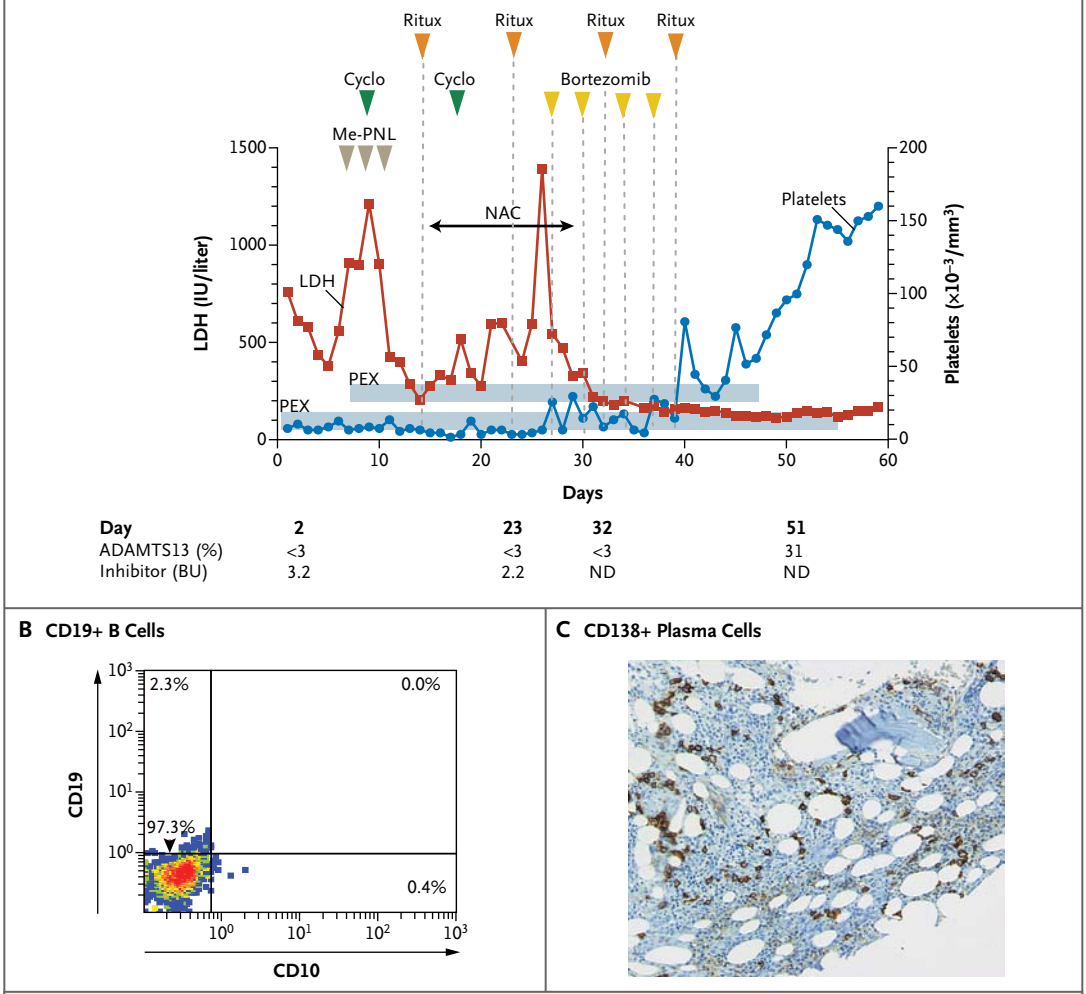

Figure 1. Major Events in the Clinical Course and Laboratory Results.

Panel A shows a timeline of the patient's clinical course, with arrows indicating points of intervention. The frequency of plasma exchange (PEX) is indicated by the gray bars, and results of laboratory testing for levels of ADAMTS13 and inhibitory autoantibodies against ADAMTS13 (inhibitor) are shown below the graph. Panel B shows flow cytometric analysis of a bone marrow–biopsy sample obtained on day 25, showing a virtual absence of CD19+ B cells. Panel C shows scattered CD138+ plasma cells identified on immunohistochemical staining of the bone marrow sample. Cyclo denotes cyclophosphamide, LDH lactate dehydrogenase, Me-PNL methylprednisolone, NAC *N*-acetylcysteine, ND not done, and Ritux rituximab.

depletion on flow cytometry (Fig. 1B). We therefore postulated that residual autoantibodies were derived from plasma cells and noted scattered CD138-positive plasma cells in the biopsy sample (Fig. 1C). After institutional review, compassionate access to bortezomib was granted, and treatment was administered according to previously published schedules for depleting alloreactive HLA antibodies in solid-organ transplantation (four doses of 1.3 mg per square meter started on day 27).[4] There was an immediate reduction in hemolysis followed by recovery of platelet counts and neurologic improvement. The patient was weaned from glucocorticoids, and plasma exchange was stopped on day 56. The patient was discharged to rehabilitation on day 60.

We hypothesize that the clinical improvement that we observed was due to bortezomib-

induced depletion of residual autoreactive B cells and plasma cells. This observation should be further evaluated in formal clinical trials.

Jake Shortt, M.B., Ch.B., Ph.D.
Danielle H. Oh, B.H.B., M.B., Ch.B.
Stephen S. Opat, M.B., B.S.

Monash Medical Centre
Melbourne, VIC, Australia
jake.shortt@southernhealth.org.au

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

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CORRECTIONS

Repackaging Cigarettes — Will the Courts Thwart the FDA? (November 29, 2012;367:2065-7). In the first sentence of the article (page 2065), "August 12, 2012" should have been "August 15, 2012," and "mouth ulcers" should have been "mouth cancer." Also, in the reference list (page 2067), reference 5 should have been "Institute of Medicine. Ending the tobacco problem: a blueprint for the nation. Washington, DC: National Academies Press, 2007," rather than "Institute of Medicine. Growing up tobacco free: preventing nicotine addiction in children and youths. Washington, DC: National Academies Press, 2007:237." The article is correct at NEJM.org.

A Tickling in the Ear (September 20, 2012;367:e17). In the second and third sentences (page e17), "tick" should have been "bug." Also, several sentences should not have been included: the sixth sentence, beginning "The tick was identified . . ."; the sentence that follows, beginning "This tick can serve"; and the final two sentences, beginning with "Serologic studies . . . ." In the eighth sentence, beginning "In addition . . . ," the words "In addition to being able to transmit disease, ticks and other" should not have been included. The article is correct at NEJM.org.

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Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal's *website (NEJM.org/medical-conference). The listings can be viewed in their entirety or filtered by specialty, location, or month.*

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The meeting, subtitled "Innate and Adaptive Immune Response and Role of Tissues in Immune Regulation," will be held in Davos, Switzerland, March 13–16.

Contact Sandra Crameri, Swiss Institute of Allergy and Asthma Research (SIAF), Obere Strasse 22, CH-7270 Davos, Switzerland; or call (41) 81 410 08 42; or fax (41) 81 410 08 40; or e-mail: wirminfo@wirm.ch; or see http://www.wirm.ch.

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