We addressed the fourth point made by Piessen et al[2] by constructing propensity scores as another adjustment method to reach what they suggest to be "comprehensively robust conclusions." HRs associated with SRCs in models including SRCs alone (HR, 1.04; 95% CI, 0.98 to 1.11; SRC plus propensity score deciles: HR, 1.01; 95% CI, 0.94 to 1.09; and SRC plus propensity score deciles plus tumor grade: HR, 1.00; 95% CI, 0.94 to 1.08) all suggest no independent contribution of SRC to mortality. Thus, the suggestions of Piessen et al further support our conclusion regarding the central role of differences in presentation between SRC and gastric AC tumors in the United States.

Finally, we note that it is unclear whether the statistical models estimated in an earlier article by Piessen et al,[3] in which mortality differences were demonstrated as a function of SRC, simultaneously adjusted for differences in presentation of the kind we adjusted for in this study. Our findings demonstrate the results from a robust national database reflecting the diversity of the population in the United States. We look forward to the results from France.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2012.47.8263; published online ahead of print at www.jco.org on April 22, 2013

Acute Oxaliplatin-Induced Thrombotic Thrombocytopenic Purpura: A Case Report and Results From a Cytoflourimetric Assay of Platelet Fibrinogen Receptor

To the Editor: In their recent article, Niu and Mims[1] described a patient with oxaliplatin-induced thrombotic thrombocytopenic purpura (TTP). Clinical evidence was supported by the ADAMTS13 (a disintegrin-like metalloprotease with thrombospondin type I motifs) metalloproteinase assay, and the authors postulated the role of an immune process as the principal underlying mechanism. We recently had a similar experience with a 68-year-old woman with liver and peritoneal metastases from colon cancer. The experimental aspect of our experience focused mainly on the sudden drop in platelet count and on the possibility of performing an affordable and dynamic platelet function test that could provide further valuable pathogenetic insights into the problem.

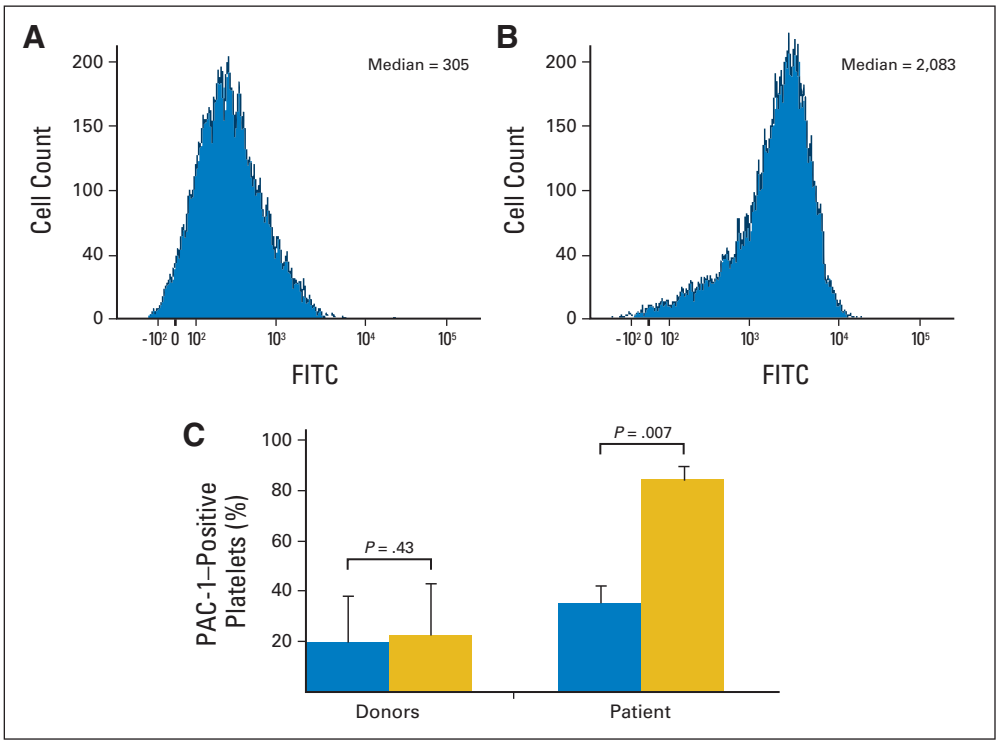

Fig 1. (A) Fluorescence intensity of PAC-1 (FITC) assessed in the patient's blood at baseline and (B) after incubation with oxaliplatin 0.5 mmol/L for 10 minutes. (C) Percentage of PAC-1–positive platelets before (blue bar) and after (gold bar) oxaliplatin incubation in three healthy donors and in the patient's blood (mean and standard deviations are reported).

The patient received adjuvant chemotherapy with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in 2006, with no adverse effects. In 2011, after evidence of relapsed disease, additional cycles of chemotherapy with FOLFOX were administered. The first two cycles were concluded with no adverse effects, and routine blood tests were normal (platelet count, 194 $\times$ $10^3/\mu$L; international normalized ratio [INR], 1.06). However, 30 minutes after the third oxaliplatin infusion, the patient experienced severe bleeding of the gums and nail beds, epistaxis, and hematuria. Vital parameters were normal.

Blood tests were repeated, with evidence of severe thrombocytopenia (platelets, 5 $\times$ $10^3/\mu$L) and increased INR (1.77). Although a more complete coagulation assay including fibrinogen, antithrombin, and D-dimer parameters was requested, the blood sample could not be processed because of rapid blood clotting in the test tube. Therefore, a platelet transfusion was given, which immediately resolved the clinical problem. A new blood sample that was taken after 18 hours showed an increase in the platelet count (33 $\times$ $10^3/\mu$L) and a decrease in INR (1.32). Blood parameters had normalized by the next day.

Whereas Niu and Mims[1] investigated the activity of ADAMTS13, we designed a method using the cytofluorimetric evaluation of anti-CD61 (integrin beta-3) and PAC-1 binding to assess oxaliplatin-induced platelet activation. PAC-1 is an antiplatelet antibody that is capable of detecting fibrinogen receptor expression after the conformational change of platelet glycoprotein IIb/IIIa.[2] Such expression is unique in the process of platelet activation. The analysis was performed on three blood samples that were obtained from the patient at different times after recovery from the acute event, and from three healthy donors. PAC-1 and anti-CD61 binding was evaluated at baseline and after 10 minutes of in vitro contact between whole blood and oxaliplatin 0.5 mmol/L, simulating the concentration during the course of chemotherapy infusion. Figure 1 shows the main outcome of the tests. Significant platelet activation ($P = .007$) was observed after exposure of the patient's blood sample to the drug, whereas PAC-1 expression remained unchanged in the healthy donor samples ($P = .43$). The analysis was repeated using fluorouracil (380 mmol/L), but without obtaining platelet activation.

Our findings show that, in our patient, oxaliplatin induced the fibrinogen receptor exposure independently of the influence of the endothelium. We agree with the conclusion of Niu and Mims[1] that the observed thrombocytopenia may have been caused by an oxaliplatin-mediated autoimmune response. Other articles have also focused on the presence—in some patients—of serum antioxaliplatin immunoglobulin G, which could represent the initial stimulus that is needed for sudden platelet activation.[3,4] Such an observation is consistent with the fact that no cases of TTP have ever been reported during the first cycle of FOLFOX.

Additional studies are needed to clarify whether the cytofluorimetric assay of PAC-1 represents a valid and inexpensive method to assess immunologic sensitization to oxaliplatin before its administration so that the dramatic clinical impact of induced TTP can be avoided.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2012.48.3248; published online ahead of print at www.jco.org on April 22, 2013

