Scott Murphy’s contribution in the early years of posttransfusion purpura: a remembrance

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Dr. Scott Murphy always enjoyed a medical mystery and his passion for the syndrome of posttransfusion purpura (PTP) was one of his favorite topics. This “perfect storm” of immunologic events is characterized by profound thrombocytopenia approximately 7 days after transfusion and includes the development of a platelet-specific alloantibody which destroys any antigen-positive transfused platelets as well as the patient’s own platelets, which lack the corresponding antigen. Dr. Murphy’s interest in this syndrome began in the early years of his research career. He also provided our laboratory with the first antiserum, which we used to develop testing procedures and to investigate numerous cases of PTP. In the next few pages of this edition dedicated in his honor, I would like to provide a brief trip down memory lane to remember his valued contribution to the Platelet Serology Laboratory at the Penn-Jersey Region of the American Red Cross (ARC) in Philadelphia, to outline some of the many advances that have taken place in the investigation of platelet antibodies, and to summarize the results of our laboratory investigation of PTP at Penn-Jersey.

I first had the pleasure of meeting Scott Murphy in the late 1970s while working as a research technologist at the Penn-Jersey Region of the ARC. At that time, we were in the process of developing a procedure to type donor platelets for the PI\textsuperscript{A} antigen. Dr. Miriam Dahlie, our medical director, informed me that Dr. Murphy had offered to share a supply of anti-PI\textsuperscript{A}, which was the result of a plasma exchange performed on a patient diagnosed with PTP. Not wanting to waste his supply for his own patients, I headed to his laboratory at the other end of town on that very hot, late spring day, armed with a box and a small supply of ice.

I was greeted by a bearded 1970s version of our own Scott Murphy, complete with heavy cotton lab coat emblazoned with his name and “Cardeza” in bright red embroidery. He appeared supremely happy in his crowded research lab as he presented me with a bag containing nearly a full liter of plasma. I remember his response after I thanked him and asked if our laboratory could do anything to return the favor. He said, “just type a lot of platelets for our patients.” I would later learn that this was his way, always a gracious gentleman who held his patients and others’ as his first priority.

As I headed back with my precious cargo, I noticed a small split in the bag and was faced with the dilemma of making it back to the ARC building before it thawed (and leaked all over Center City Philadelphia). The just-in-time arrival of an available taxi cab allowed me to beat the clock and the weather. I have to admit that this was, unquestionably, the only time in my career that, while working late into the evening, the usually boring task of preparing a thousand tiny 1-mL vials was pure pleasure.

In 1975, while on the staff of the Hematology Research Laboratory at the Presbyterian-University of Pennsylvania Medical Center in Philadelphia, Dr. Murphy coauthored a seminal publication calling attention to the variety of responsible antibodies and patient profiles in the relatively newly described and clinically mysterious syndrome of PTP. Before the publication of this paper in 1975, all of the 14 described cases of PTP were attributed to the presence of anti-PI\textsuperscript{A} produced by PI\textsuperscript{A}-negative female patients. Two of the three patients described in this paper (one PI\textsuperscript{A}-negative man who produced anti-PI\textsuperscript{A} and a PI\textsuperscript{A}-positive woman with a demonstrable anti-platelet antibody of unknown specificity) served to expand the definition of PTP to include both male and female patients with antibody specificities not limited to anti-PI\textsuperscript{A}.
PTP is a relatively rare, but well-defined, syndrome first described by Shulman et al. in 1961.2 The classic patient profile describes an older, multiparous woman with a precipitous, antibody-mediated drop in platelet count occurring 7 to 10 days after transfusion. Unlike the maternal antibodies responsible for neonatal alloimmune thrombocytopenia, the antibodies produced by patients diagnosed with PTP cause severe thrombocytopenia in the antibody producer. PTP is self-limiting, but carries a significant risk of fatal hemorrhage. Similarities have been noted between PTP and the hemolysis of autologous RBCs during delayed hemolytic transfusion reactions caused by some RBC antibodies.3 To date, there is no definitive explanation for the destruction of autologous cells in either situation. In the years after Dr. Murphy’s 1975 publication and since the first description of a platelet-specific antigen by van Loghem in 1959,4 much has been learned about the nature of platelet antigens. The nomenclature for platelet-specific antigens was standardized by a Working Party on Platelet Serology5 (Table 1) and adopted by the International Society of Blood Transfusion. In this more orderly, numeric system, the platelet antigens are designated as HPA (human platelet antigens) and are numbered (with Arabic numbers) according to discovery date, followed by a lower case “a” or “b,” which denotes the high (a) or low (b) frequency member of the antigen pair. As an example of the need for simplification, the first antigen reported was referred to as Zwα in Europe and Plα1 in the United States. Under the new nomenclature, it is now called HPA-1a. Its lower frequency allele (Plα2 or Zwβ) is now HPA-1b. We now know that six platelet-specific antigen systems (HPA-1 through 5 and HPA-15) are biallelic with one high frequency and one low frequency antigen or allele.6 For the remaining 10 antigens (HPA-6 through 14 and HPA-16), alloantibodies against the low frequency but not the high frequency antigen have been observed. The molecular basis and location on the platelet membrane has been resolved for antigens listed in Table 1. With the exception of HPA-14, the differences in the alleles are the result of a single amino acid substitution at a specific location on the gene encoding for the membrane glycoprotein. The isoantigen, Nakα,7 is now known to be located on GPIV (CD36).89 These advances, as well as the availability of monoclonal antibodies, which recognize specific glycoprotein locations on the platelet surface, have led to the development of serologic testing techniques with increased sensitivity10–14 as well as to the development of molecular techniques15 for platelet antigen typing. Other specificities have since been identified as pathogenic antibodies in PTP using a variety of investigative techniques. These include anti-Plα2 (HPA-1b),16 anti-Bakα (HPA-3α),17 anti-Bakβ (HPA-3b),18 anti-Penα (HPA-4a),19 anti-Brα (HPA-5b),20 and anti-Brβ (HPA-5a).21,22

In 1992, Dr. Murphy became the medical director of the Penn-Jersey Region, and we had the honor of working with him for the next 14 years. His fascination with the syndrome of PTP and his concern for the patients involved never waned. He was never too busy to make time in his schedule to learn the details of each new case. He would then consult directly with the patient’s clinician to ensure that our center could provide appropriate testing, consultation, and transfusion support. Options for transfusion support,
when needed, would vary from case to case and might include antigen-negative single-donor platelets or washed or deglycerolized RBCs.

Since 1983, our laboratory has investigated 115 patient samples submitted to rule out PTP. Samples were tested for the presence of platelet-specific and HLA antibodies using a variety of methodologies. Of 115, 33 (28.6%; 31 from women, 2 from men) contained platelet-specific antibody(ies) and these patients were diagnosed with PTP based on this finding along with clinical history. Of these, 23 demonstrated anti-HPA-1a, 4 anti-HPA-1b, 3 anti-HPA-3a, 1 anti-HPA-1b and anti-HPA-3a, 1 anti-HPA-5b, and 1 anti-HPA-5a (Fig. 1). Molecular testing was used to confirm the antigen-negative status in five cases. Nineteen were confirmed using serologic techniques on postrecovery platelet samples. Nine were not submitted or were unavailable for confirmation. Of note is the fact that 23 of the 33 (69.6%) sera also demonstrated HLA class I antibodies in combination with platelet-specific antibodies, indicating the necessity to use glycoprotein-based as well as standard whole-cell methods as part of the investigative protocol to ensure detection of coexisting antibodies. Of the remaining 82 samples, the majority either were negative or demonstrated HLA antibody only. These results, along with other published data, support Dr. Murphy’s early report of the heterogeneous nature of PTP.

Thank you, Scott Murphy, for your support, sustained enthusiasm, and undiminished desire to help patients in need. You are missed by everyone here at the ARC. As I anticipate further advances in the challenging fields of platelet testing and transfusion, I will not forget that happy, bearded researcher of many years ago, and I am delighted to report that the plasma handed to me 29 years ago remains in use in our laboratory and continues to help so many of “our patients.”

References


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