

Neutropenia and monocytopenia in recurrent anaphylactoid reactions after red blood cell transfusions in a woman with immunoglobulin A (IgA) deficiency and anti-IgA

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BACKGROUND: Transfusion-associated anaphylaxis has been associated with anti-immunoglobulin A (anti-IgA) of IgG class in patients with IgA deficiency. In recent years, however, the frequency and clinical impact of this syndrome has been questioned. We present a case of recurrent red blood cell (RBC) transfusion-associated anaphylactoid reactions (rigors, hypertension, transient monocytopenia, and neutropenia) associated with anti-IgA.

CASE REPORT: An 88-year-old woman developed anemia after a traumatic right humerus fracture. After receiving approximately 100 mL of RBCs she developed rigors and hypertension; her absolute neutrophil and monocyte counts decreased by 73 and 100%, respectively. All symptoms and signs resolved, and her blood counts normalized. A second RBC transfusion was given, with recurrence of rigors, hypertension, neutropenia, and monocytopenia (69 and 100% declines, respectively), along with fever. All tests for hemolysis were negative. She then received two transfusions of washed RBCs, without incident. The patient was found to be deficient in IgA (<0.05 mg/dL). Further, anti-IgA of IgG class antibodies were detected in high levels by enzyme-linked immunosorbent assay (>1000 U/mL). We reviewed case reports, case series, and reviews of IgA deficiency-associated reactions, examining whether hypertensive reactions and acute neutropenia and/or monocytopenia have been associated with anti-IgA reactions.

RESULTS: Reports of reactions associated with anti-IgA emphasize hypotension and are generally classified as “anaphylactic or anaphylaxis.” No previous reports described neutropenia or monocytopenia.

CONCLUSION: Our case suggests that adverse transfusion reactions associated with anti-IgA of IgG class may sometimes be characterized by anaphylactoid features such as rigors and hypertension, with transient monocytopenia and neutropenia.

Authoritative reviews¹ or book chapters^{2–4} describing transfusion reactions typically include those associated with anti-immunoglobulin A (anti-IgA) in the allergic or anaphylaxis category. First described in 1968,⁵ patients developed dermal reactions (urticaria, erythema) and/or anaphylaxis (hypotension, cardiovascular collapse, wheezing) after receiving blood, plasma, or gamma globulin; the authors found evidence for anti-IgA with underlying IgA deficiency. With the appearance of a few dozen subsequent reports, by 1995 the syndrome of “IgA anaphylactic transfusion reactions” seemed established.⁶

However, the concept of transfusion-associated anaphylaxis associated with anti-IgA and IgA deficiency has recently been challenged. In an article entitled “The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based,” Sandler and coauthors⁷ pointed out that national hemovigilance programs in the United States (2003–2012) and Canada (2008–2012), evaluating patients with transfusion-associated allergy or anaphylactic reactions, have only rarely identified patients with anti-IgA alloantibodies and/or IgA deficiency. Further, their review of 229 allergic or severe anaphylactic reactions reported in published national hemovigilance

ABBREVIATION: PaGIA = particle gel immunoassay.

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Received for publication April 23, 2018; revision received June 14, 2018; and accepted June 16, 2018.

doi:10.1111/trf.14894

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TRANSFUSION 2018;00;1–6

studies identified only three (1.3%) patients who had absent IgA with anti-IgA.⁷ Even if anaphylactic reactions are only rarely (if at all) associated with anti-IgA, the possibility exists that other types of transfusion reactions might be caused by anti-IgA, as suggested by the following case.

CASE REPORT

An 88-year-old woman was admitted to hospital because of right humerus fracture sustained from a fall. Her past medical history was remarkable for chronic hypertension (treated with candesartan and hydrochlorothiazide) and dyslipidemia (atorvastatin). She had undergone total hip arthroplasty 2 years earlier, with postoperative myocardial infarction, and so she was also receiving long-term treatment with aspirin (81 mg daily) and dabigatran (110 mg twice daily). After the fracture, her admission hemoglobin (Hb) level was 9.5 g/dL, which decreased to 7.2 g/dL, believed secondary to fracture site bleeding possibly exacerbated by antiplatelet (PLT) and anticoagulant therapy. She had no known prior blood transfusions. She had four pregnancies without complications. She was group B, D+, with no red blood cell (RBC) alloantibodies.

Three days before scheduled orthopedic surgery, she began to receive 1 unit of RBCs (group B, D+). One hour after beginning transfusion (91 mL of product transfused), she developed dramatic rigors ("shaking so hard I couldn't use the call bell"). She also complained of nausea, but denied headache, back pain, sweating, and dyspnea. Assessment showed tachycardia (heart rate increase from 81/min before transfusion to 111/min), hypertension (from 123/66 to 152/91 mmHg), but with minimal temperature elevation (peak, 37.3°C). No urticaria, flushing, wheezing, or other abnormalities were observed. Workup by the transfusion medicine laboratory revealed no evidence for a hemolytic transfusion reaction (clerical check unremarkable, no visible hemolysis, direct antiglobulin test negative). In addition, cultures of the residual RBCs grew no organisms. The patient recovered completely within 1 hour.

The next day the patient began to receive a second RBC unit (group B, D+). Fifty-five minutes after beginning transfusion (100 mL of product transfused), the patient developed a strikingly similar reaction as on the previous day, featuring once again severe rigors, tachycardia (heart rate increase from 82/min to 162/min), hypertension (132/64 to 168/90 mmHg), but now also with documented fever (38.5°C). Once again, no urticaria, flushing, or wheezing were observed. The patient recovered completely within 1 hour. Repeat workup by the transfusion medicine laboratory again revealed no evidence for a hemolytic transfusion reaction; blood cultures of the residual RBCs concentrate again grew no organisms.

Hematology consultation was obtained; reviewing serial complete blood counts, the hematologist identified dramatic decreases in white blood cell (WBC) levels, including transient neutropenia (abrupt approx. 75% declines in neutrophils [from 6.6×10^9 to 1.8×10^9 /L; from 9.0×10^9 to 2.8×10^9 /L]), with profound monocytopenia (abrupt 100% decline in monocytes to undetectable levels [from 0.9×10^9 to 0×10^9 /L], on both occasions), in association with each of the two transfusion reactions (Fig. 1). In addition, circulating normoblasts (nucleated RBCs) were seen transiently after each transfusion (quantitated at two nucleated RBCs per 100 WBCs).

The patient was then transfused with 2 units of washed RBCs. No reactions occurred and a satisfactory increase in Hb was noted.

MATERIALS AND METHODS

Patient serum was referred to Canadian Blood Services for measurement of IgA levels and detection of anti-IgA. Immunoglobulin levels were measured by nephelometry and rapid particle gel immunoassay (ID-PaGIA IgA deficiency test, Bio-Rad Laboratories, DiaMed GmbH). Detection of anti-IgA was performed using two tests, the ID-PaGIA anti-IgA test (Bio-Rad Laboratories, DiaMed GmbH), as well as an IgG-specific enzyme-linked immunosorbent assay (ELISA, performed at Viracor IBT Laboratories).

Literature review

We conducted a literature search of English language articles published between August 1968 and March 2018 using PubMed, entering combinations of the keywords "IgA" or "immunoglobulin A" and "transfusion" or "transfusion reaction." Additional studies were identified by manually searching the references of included studies and related reviews. The literature search was conducted by one author (PAM). We specifically focused on identifying cases reporting hypertension and/or transient leukopenia (neutropenia or monocytopenia). To satisfy inclusion criteria, articles needed to describe one or more cases of reactions to blood product(s) where an anti-IgA had been identified and with sufficient clinical data to permit evaluation.

RESULTS

IgA level and presence of anti-IgA

The patient had undetectable levels of IgA (<7 mg/dL [reference range, 70–352 mg/dL]) by nephelometry. Normal levels of IgG (1080 mg/dL [reference range, 635–1465 mg/dL]) and mildly reduced levels of IgM (29 mg/dL [reference range, 41–207 mg/dL]) were found. Using the ID-PaGIA assay, IgA levels were less than 0.05 mg/dL and anti-IgA were detected; using ELISA, anti-IgA of IgG subclass were also

identified, at a level of more than 1000 U/mL (normal, <99 U/mL).

Literature review

The initial literature search (Fig. 2) identified 576 articles, most of which could be excluded by screening the title and/or abstract. After screening, 26 articles were selected for full-text review. Of these, 12 articles providing clinical and laboratory details on 35 cases were identified,^{5,8–18} of which five were identified through manual search of references. None mentioned the occurrence of neutropenia or monocytopenia. Only two cases mentioned hypertension,^{9,13} one of which was quickly followed by hypotension.

DISCUSSION

This case report describes an unusual reaction to 2 RBC units in the same patient, in association with detection of high levels of IgG anti-IgA. The reactions are associated with an anomaly in the recipient, as almost identical reactions occurred with products from two different donors; reactions such as transfusion-associated lung injury or transfusion-related alloimmune neutropenia are therefore most unlikely, as they are caused by donor alloantibodies within the product transfused. (Indeed, the Canadian Blood Services declined to perform donor investigations based on this clinical history.) Furthermore, washed units caused no reaction, suggesting the patient reacted to an element present in the plasma of both donors. IgA levels were unequivocally reduced, and presence of anti-IgA of IgG subclass was confirmed, making it plausible that these antibodies were responsible for the reaction. For both reactions, a similar amount of RBC product was transfused (91 and 100 mL), suggesting that a certain amount of protein, in this case IgA, was required to result in formation of sufficient amounts of IgG anti-IgA/IgA immune complexes, to trigger the reaction.

Definitions and clinical features of anti-IgA-associated reactions were reviewed in transfusion medicine textbooks. *Mollison's Blood Transfusion in Clinical Medicine*² describes reactions associated with anti-IgA as causing "such symptoms as dyspnea, substernal pain, laryngeal edema and circulatory collapse," in patients with undetectable IgA and high-titer anti-IgA. Popovsky's *Transfusion Reactions*³ includes anti-IgA-associated reactions in the "Allergic and Anaphylactic Reactions" chapter, describing these reactions as anaphylactic or anaphylactoid, with a typical allergic/anaphylactic clinical picture. Rossi's *Principles of Transfusion Medicine*⁴ defines IgA-associated reactions as "anaphylactoid" due to their underlying (non-IgE-mediated) mechanism, but considers them to be identical as anaphylactic reactions from a clinical standpoint. None of these textbooks mentions hypertension or leukopenia as possible consequences of anti-IgA-associated reactions.

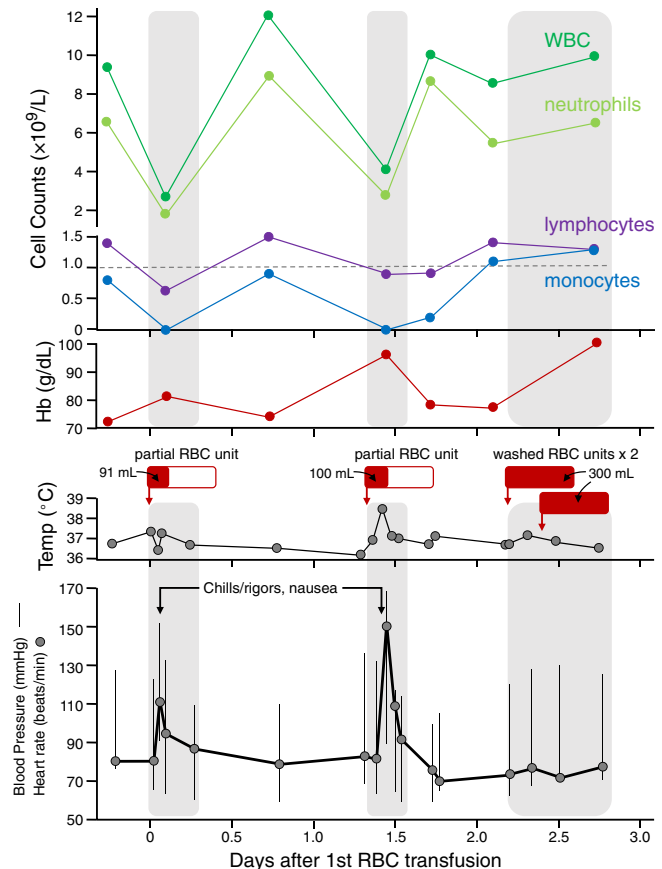


Fig. 1. Time course and clinical picture of two anaphylactoid reactions associated with transfusion of RBCs. Four panels (described from top to bottom) show (A) that transient leukopenia (moderate neutropenia, severe monocytopenia) occurred in association with both transfusion reactions; (B) serial Hb values; (C) serial temperature values; and (D) vital signs and clinical features of two transfusion reactions associated with transfusion of 91 and 100 mL of RBCs. The gray-shaded areas shown in all panels correspond to the period of clinical evaluation after each transfusion episode. No adverse events occurred after transfusion of washed RBCs. Subsequently, the patient was shown to be deficient in IgA and to have high levels of anti-IgA of IgG class (see text for details). The reduced absolute neutrophil counts after the two transfusion reactions (1.8 and 2.8, respectively) were outliers: review of 25 other complete blood counts (CBCs) for this patient between 2008 and 2017 showed the following values for the absolute neutrophil counts: median, 6.5 (interquartile range [IQR], 4.7–9.6; range, 2.2–11.6). Further, the severely reduced absolute monocyte counts after the two transfusion reactions (both measuring 0) were distinct outliers: review of 25 other CBCs for this patient between 2008 and 2017 showed the following values for the absolute monocyte counts: median, 0.8 (IQR, 0.6–1.0; range, 0.5–1.3). [Color figure can be viewed at wileyonlinelibrary.com]

The first report of probable reactions associated with anti-IgA in IgA-deficient patients was published in 1968.⁵ In this series, Vyas and colleagues described six patients who

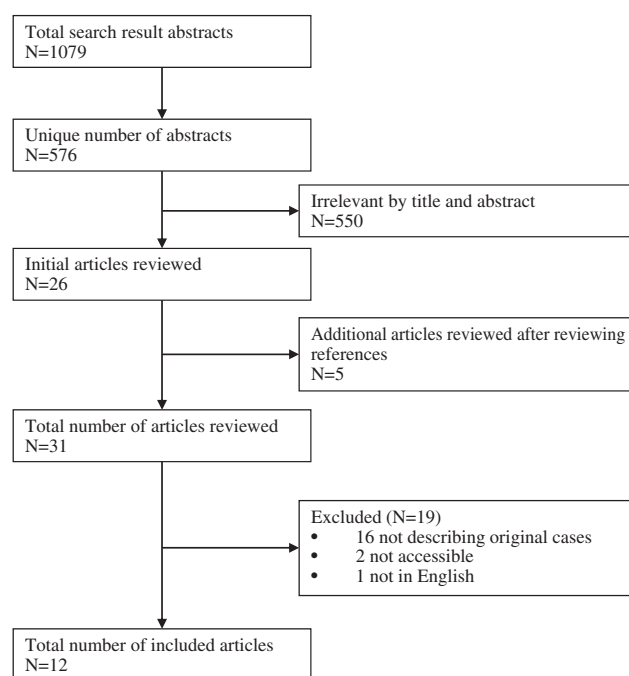


Fig. 2. Literature search flowchart.

received blood transfusions, plasma infusions, or intramuscular injections of immunoglobulins. Of these, three patients experienced classic, severe anaphylactic reactions and were found to have nondetectable IgA levels and class-specific anti-IgA with broad reactivity. The three others experienced less severe “anaphylactoid” reactions, without hypotension, and had anti-IgA of limited specificity in their serum. They also had detectable (normal or slightly decreased) IgA levels. These anaphylactoid reactions were described as diffuse skin rash in two patients and as a combination of tachycardia, pallor, discomfort, and dyspnea in another. None reportedly had hypertension or rigors.

Other case series were published in the next years describing patients with reactions believed to be associated with anti-IgA. In 1973, a Finnish series¹⁰ described four patients with typical anaphylactic reactions with hypotension after transfusion in patients with IgA deficiency and an anti-IgA. Another series from 1975 described four patients with anaphylactic reactions associated with hypotension including one death, again with anti-IgA; two of the cases had normal IgA levels.¹² In 1984, a Canadian series¹⁶ described reactions involving whole blood, RBCs, plasma, and PLTs in 10 patients with anti-IgA; five had hypotension, and all 10 fulfilled criteria for anaphylaxis.

The other reports^{8,9,11,13–15,17,18} we reviewed each described one or two cases; none of the patients described in these reports appeared to have the same combination of clinical findings as in our patient, mainly a combination of shaking chills, mild to moderate pyrexia, hypertension, and transient leukopenia (neutropenia, monocytopenia). Rather, hypotension was a common clinical feature. Most of them

had clear allergic symptoms, such as an urticarial rash, digestive symptoms, or respiratory compromise, and a majority fulfilled the criteria to be defined as anaphylaxis. No report listed neutropenia or monocytopenia as a feature.

Among all the reports we reviewed, we identified only one case where hypertension was part of the clinical picture.¹³ A 15-year-old female with hypogammaglobulinemia without detectable IgA developed cyanosis and dyspnea after 15 mL of ABO-compatible plasma, followed by severe lower abdominal pain. This was accompanied by “moderate hypertension and a tachycardia” (no values provided) for a duration of 45 minutes, and her vital signs returned to normal within 45 minutes without specific therapy. No urticaria or angioedema were noted. She was found to have IgG antibodies against IgA with a titer of 640.

Although the initial report of transfusion reactions associated with IgA deficiency and anti-IgA called these reactions “anaphylactoid,” most classifications refer to them as “anaphylaxis/anaphylactic.” The latter term includes hypotension in the group of symptoms and signs. Our patient’s reaction clearly involved hypertension, rather than hypotension; further, other features of anaphylaxis (bronchospasm, laryngeal edema, erythema/urticaria) were not seen. Additionally, striking transient declines to profound neutropenia and monocytopenia were identified. It is possible that transient neutropenia and/or monocytopenia could occur in some patients who form IgG-containing immune complexes but that these cytopenias are not noticed, either because complete blood counts are not performed during the anaphylactoid reaction or because the transient blood count declines are not noted by the clinician.

The validity of the association between anti-IgA in IgA-deficient patients and anaphylactic transfusion reactions has recently been questioned.⁷ Due to the rarity of anaphylaxis after transfusion, this entity is difficult to study and poorly validated, but has been assumed to exist; however, testing for anti-IgA is regularly performed, and IgA-deficient blood products are used in patients, sometimes even as primary prevention. Unfortunately, IgA and anti-IgA testing are not always requested after an anaphylactic reaction, which limits the interpretability of data. When they are performed, only a minority of patients have anti-IgA. For example, the American Red Cross National Reference Laboratory reported in 1994 that among 359 patients who were tested for anti-IgA after an anaphylactic transfusion reaction, only 61 (17%) were IgA deficient and had an anti-IgA.¹⁹ IgA deficiency is a common condition, with an estimated prevalence of one in 560 donors;²⁰ prevalence of both deficiency and anti-IgA is estimated at one in 1560. The authors of this commentary have estimated that if anti-IgA were sufficient to cause anaphylactic reactions and that the prevalence of IgA deficiency was equivalent in recipients and donors, 48 anaphylactic transfusion reactions would occur every day in the United States,⁷ casting doubt on the association between anti-IgA and anaphylaxis.

The distinction between anaphylactic (hypotensive) and anaphylactoid (hypertensive) reactions has been made in the literature pertaining to distinct syndromes of adverse reaction seen with heparin.²¹ Heparin-induced “anaphylaxis” is a clinical feature of reactions caused by heparin adulterated with oversulfated chondroitin sulfate, which caused an epidemic of life-threatening and fatal *hypotensive* reactions; the pathogenesis involves generation of bradykinin through contact system activation by oversulfated chondroitin sulfate. In contrast, immune reactions featuring antibodies of IgG class against PLT factor 4/heparin complexes, implicated in heparin-induced thrombocytopenia, feature reactions that include fever, chills, tachycardia, and *hypertension*.²¹ These reactions involve RBC-activating antibodies of IgG class, although the mechanisms by which such hypertension-producing “anaphylactoid reactions” associated with heparin bolus administration cause hypertension and fever are not known. The key point, however, is that heparin-induced anaphylaxis versus heparin-induced anaphylactoid reaction involve distinct pathogeneses (bradykinin generation versus IgG-mediated cellular activation, respectively).

CONCLUSIONS

The unique clinical and laboratory picture of our case has several possible implications. First, it is possible that anti-IgA reactions in some cases might mimic somewhat febrile nonhemolytic transfusion reactions (as in our case), but because the current literature emphasizes anaphylaxis and/or anaphylactic hypotensive reactions, physicians might not test for IgA deficiency and anti-IgA in this clinical context. Second, our patient’s anti-IgA are of IgG class, and formation of IgG anti-IgA/IgA immune complexes is a plausible explanation for activation of neutrophils and monocytes through their high-affinity IgG Fcγ receptors.²² On the other hand, it is possible that our patient’s clinical picture is unique and will not be recapitulated in other patients with reactions mediated by anti-IgA. Moreover, we cannot exclude the possibility that our patient’s recurrent transfusion reactions were unrelated to the presence of high-titer anti-IgA and may have been the result of another obscure cause. However, despite the presence of anti-IgA in the general population being fairly common (one in 1560 in donor populations²⁰), titers higher than 1000 U/mL—as observed in our patient—are less frequent, representing only approximately 11% of positive samples (personal communication, Viracor IBT Laboratories, 2018). Thus, the high anti-IgA level of more than 1000 U/mL found in our patient would be expected to be present in only approximately one in 14,000 individuals. Given the current controversy regarding the existence and clinical picture of anti-IgA transfusion reactions,⁷ our case report might provide insights into the possible clinical spectrum of this entity.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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