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Autoimmune hemolytic anemia and thrombocytopenia attributed to an intrauterine contraceptive device

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Abstract

BACKGROUND—Evans syndrome is a rare condition manifested by combined autoimmune hemolytic anemia (AIHA) and thrombocytopenia or neutropenia. It is often associated with other autoimmune disorders, immunodeficiencies, and non-Hodgkin's lymphoma.

CASE REPORT—We describe a patient with Evans syndrome that may have been related to exposure to a polyethylene-based intrauterine contraceptive device (IUD). A 26-year-old white female presented with severe, symptomatic AIHA and subsequently developed severe thrombocytopenia. She had a refractory course resistant to multiple treatments including corticosteroids, intravenous immune globulin, rituximab, splenectomy, cyclophosphamide, cyclosporine, eculizumab, and plasma exchange. It was then noticed that her serum autoantibody agglutinated red blood cells (RBCs) in the presence of polyethylene glycol (PEG) but not in the absence of PEG nor when an alternative agglutination enhancing technique, low-ionic-strength solution, was used. Therefore, her polyethylene-containing IUD, which was a polyethylene frame with a levonorgestrel-releasing device, was removed. Norgestrel-dependent, platelet (PLT)-reactive antibodies were not identified by either flow cytometry or in vivo in a NOD/SCID mouse. Testing for PEG-dependent antibodies was not possible. Remission, with no requirement for RBC or PLT transfusions and return of her hemoglobin and PLT counts to normal, followed removal of the IUD.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

CONCLUSION—The patient's recovery after removal of the IUD and the PEG dependence of RBC agglutination suggested a possibility that the IUD may have been a contributing factor to the etiology of Evans syndrome in this patient.

Evans syndrome, manifested by combined auto-immune hemolytic anemia (AIHA) and thrombocytopenia or neutropenia, is often associated with other autoimmune disorders, immunodeficiencies, and non-Hodgkin's lymphoma; a drug-induced etiology was not mentioned in the report of 68 patients from eight French and Italian centers over 17 years.[1] Although unmaintained remissions are uncommon, 60 (88%) of the 68 patients in this report had a partial or complete response to immunosuppressive agents or splenectomy.[1] We describe a patient with Evans syndrome (AIHA and thrombocytopenia) who was refractory to continuous treatment with multiple, intensive immunosuppressive regimens and splenectomy for 11 weeks. It was then noticed that her serum autoantibody agglutinated red blood cells (RBCs) in the presence of polyethylene glycol (PEG) but not in the absence of PEG or when an alternative agglutination enhancing technique, low-ionic-strength solution, was used. Therefore, her polyethylene-containing intrauterine contraceptive device (IUD) was removed. Remission, with no requirement for RBC or platelet (PLT) transfusions and return of her hemoglobin (Hb) and PLT counts to normal followed removal of the IUD.

CASE REPORT

A 26-year-old white woman presented with weakness and jaundice in February 2012. Her Hb was 4.5 g/dL, white blood cell (WBC) count 9×10^9/L (absolute neutrophil count, 6.99×10^9/L), and PLT count 144×10^9/L; the direct antiglobulin test was strongly positive. The peripheral blood smear demonstrated no fragmented RBCs or immature or abnormal WBCs. She had had Hodgkin's disease (Stage IIB) diagnosed 1 year previously and completed ABVD chemotherapy in September 2011. She did not have a stem cell transplant. She had an IUD inserted in August 2011. Evaluation at the time of her presentation detected no evidence of recurrent Hodgkin's disease, based on a normal PET scan and marrow biopsy. There was no evidence for other lymphoproliferative or autoimmune disorders, immunodeficiency, hepatitis C, or other infections.[1] Evaluations for possible etiologies of hemolytic anemia and thrombocytopenia included flow cytometry testing for paroxysmal nocturnal hemoglobinuria; RBC glucose-6-phosphate dehydrogenase and pyruvate kinase activities; vitamin E and B_{12} levels; folate, homocysteine, methylmalonic acid, zinc, copper, arsenic, and lead levels. All tests were normal or negative. Testing for anti-nuclear antibodies and anti-neutrophil cytoplasmic antigen were negative. Testing for leishmaniasis, *Clostridia*, *Bartonella*, hepatitis B, parvovirus immunoglobulin M, and human immunodeficiency virus were negative. Drug-dependent antibodies (testing by flow cytometry with ciprofloxacin, piperacillin, sulfamethoxazole, tazobactam, trimethoprim, and vancomycin) reacting with PLTs or RBCs were not detected.

During her initial 4 weeks of hospitalization, she required transfusion of 1 to 5 RBC units on most days. During her fourth week of hospitalization, her PLT count decreased to 45×10^9/L and after this time she remained thrombocytopenic, receiving PLT transfusions for PLT counts of less than 20×10^9/L. Granulocyte counts remained normal or high throughout her hospitalization, probably related to the continuous treatment with corticosteroids.

For the first 11 weeks of her hospitalization, preceding the IUD removal, her clinical course was unaffected by treatment with multiple modalities. She continued to receive RBC transfusions on most days, averaging approximately 2 units of RBCs per day, and PLT transfusions at least once per week. She received daily oral prednisone; one course of methylprednisolone, 1000 mg/day for 3 days; five infusions of intravenous immune globulin (0.5 g/kg); and four infusions of rituximab (375 mg/m^2 × 3, 500 mg/m^2 once). She had a splenectomy, received one infusion of cyclophosphamide (1.5 mg/m^2), received two infusions of eculizumab (900 mg), received cyclosporine (250 mg, twice daily) for 12 days, and received 25 plasma exchange treatments with fresh-frozen plasma.

In the 11th week of her treatment, it was reported that her serum RBC autoantibody (panagglutinin) did not react with RBCs in the absence of PEG. In the presence of PEG ("Gamma PeG" reagent, Immucor, Inc., Norcross, GA), the agglutination titer was 256 (Table 1).[2] Testing for agglutination in the presence and absence of PEG had not been previously performed. PEG was then suspected of also potentiating the patient's in vivo hemolysis (and thrombocytopenia) and therefore her IUD (Mirena, Bayer HealthCare Pharmaceuticals, Whippany, NJ), which has a polyethylene frame with a levonorgestrel-releasing system, was removed. After IUD removal she continued to receive daily oral prednisone. She also received alemtuzumab (30 mg/day for 4 days beginning on Day 5 after IUD removal) and then daily oral cyclophosphamide (100 mg/m^2) for 3 weeks and one infusion of vincristine (1 mg). The titer of RBC agglutination in the presence of PEG had significantly decreased by Day 6 after removal of the IUD.

She required no more PLT transfusion after Day 4 after IUD removal and no more RBC transfusions after Day 20 following IUD removal. During the 20 days after IUD removal she received 16 RBC units and two PLT transfusions. In contrast, during the 20 days preceding IUD removal, she had received 39 RBC units and six PLT transfusions. Her PLT count increased to 120 × 10^9/L 20 days after IUD removal and her Hb increased to 8.5 g/dL 32 days after IUD removal, when she was discharged from the hospital; her Hb was 13.1 g/dL 26 days later (Table 1). She has remained well since her hospital discharge (through April 2014).

Our patient's serum was tested at the BloodCenter of Wisconsin (Milwaukee, WI) for norgestrel-dependent, PLT-reactive antibodies both by flow cytometry[3] and in vivo in a NOD/SCID mouse.[4] No norgestrel-dependent, PLT-reactive antibodies were identified. Testing for PEG-dependent antibodies reactive with RBCs or PLTs was not possible with these methods.

DISCUSSION

Drug (or other substance)-induced Evans syndrome has rarely been reported. We searched the authors' files and 10 databases, including Medline and PubMed, to identify articles published through February 2014 using three search strategies: 1) the MeSH terms *autoimmune hemolytic anemia* and *thrombocytopenia* with the attached subheading *chemically induced* and 2) the keyword *Evans* syndrome. A total of 443 articles were identified; 13 articles were selected for review that had drug or vaccine-induced Evans

syndrome or AIHA together with thrombocytopenia or neutropenia in their title. Using previously established criteria for assessing a causal relation between a drug and thrombocytopenia,[5] two articles presented evidence supporting a definite association of the drug with Evans syndrome.[6,7] Acetaminophen caused two episodes of acute hemolytic anemia and thrombocytopenia 8 months apart.[6] Acute pancytopenia followed exposure to oxaliplatin; evaluation documented oxaliplatin-dependent antibodies reactive with RBCs, neutrophils, and PLTs.[7] These observations document that Evans syndrome can be caused by drug-dependent antibodies. We also searched for an association of PEG with thrombocytopenia or AIHA; only articles describing adverse effects of PEG-interferon were identified. Additional searches identified three reports of hemolysis and/or thrombocytopenia associated with other organic chemical exposures: ethylene oxide,[8] polyethylene,[9] and polydimethylsiloxane.[10]

Our hypothesis is that this patient's IUD contributed to the pathogenesis of her Evans syndrome and that its removal contributed to her recovery. Our suspicion is supported by her recovery after IUD removal and by the PEG-dependence of her panagglutinin autoantibody for in vitro RBC agglutination. The observation that RBC agglutination occurred only in the presence of PEG does not indicate that the antibodies were specifically dependent on PEG. This observation can only suggest a possible relation to the IUD. There are alternative explanations for this patient's recovery. Treatment with alemtuzumab in the week after IUD removal and subsequent cyclophosphamide and prednisone treatment for 3 additional weeks may have contributed to recovery. Also, it is possible that she responded to the accumulation of all treatments during the 11 weeks preceding IUD removal in addition to the treatments she received after IUD removal.

In conclusion, our experience suggests a possibility that the presence of an IUD may be a source of materials or hormones that can contribute to the pathogenesis of immune-mediated disorders.

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ABBREVIATIONS

AIHA	autoimmune hemolytic anemia
IUD	intrauterine contraceptive device

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TABLE 1

RBC agglutination titers in the presence of PEG after removal of IUD related to clinical improvement*

	Patient serum dilutions										
Days after removal of IUD	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**Clinical observations**
0	3+	3+	3+	3+	3+	3+	2+	1+	W+	0	IUD removed; Hb, 4.7 g/dL
1											PLT count, 19 × 10^9/L; PLT transfusion
4											PLT count, 17 × 10^9/L; last PLT transfusion
6	3+	3+	3+	3+	3+	2+	1+	0	0	0	PLT count, 37 × 10^9/L
14	3+	3+	3+	3+	2+	W+	0	0	0	0	PLT count, 120 × 10^9/L
20	3+	3+	3+	2+	1+	0	0	0	0	0	Hb, 5.5 g/dL; last RBC transfusion
26	3+	3+	2+	1+	0	0	0	0	0	0	PLT count, 286 × 10^9/L; Hb, 7.4 g/dL
32											Hb, 8.5 g/dL
58											Hb, 13.1 g/dL

* RBC agglutination was determined by tube testing with PEG (Gamma PeG reagent, Immucor, Inc.) as an enhancement additive. No agglutination occurred when low-ionic-strength enhancement (N-HANCE reagent, Immucor, Inc.) was used or when no enhancement techniques were used, even in patient serum with no dilution.

W+ = weakly positive.