CASE REPORT

Post-transfusion purpura in a patient with HPA-1a and GPIa/IIa antibodies

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SUMMARY

Post-transfusion purpura is a rare bleeding disorder characterized by severe and sudden thrombocytopenia within 3–12 days after blood transfusion. Typically, preformed antibodies directed against human platelet antigens, especially HPA-1a, are associated with the clinical symptoms. A 46-year-old female presenting to the hospital with acute progressive kidney insufficiency and anaemia received two units of packed red blood cells (RBC) within 2 days. On day 7, platelet count fell from 414 to 189 x 10^9 L^-1 and 1 day later dropped to 4 x 10^9 L^-1. Four platelet concentrates were applied without success. After serological confirmation of an HPA-1a antibody, the patient was treated with intravenous gamma immunoglobulin (ivIgG), and the platelet count increased to normal values on day 17. In addition to the persisting HPA-1a alloantibody, an antibody reactive with GPIa/IIa of HPA-5a- and HPA-5b-positive platelets was detected during the acute phase of thrombocytopenia. After complete remission, the patient was transfused with four units of packed RBC from HPA-1a-negative donors, and platelet counts remained normal.

Key words: GPIa/IIa antibody, HPA-1a antibody, platelets, post-transfusion purpura (PTP).

Post-transfusion purpura (PTP) is a rare but severe bleeding disorder usually occurring 3–12 days post-transfusion of cell containing blood components. Preferentially, whole blood and red blood cell (RBC) units are involved, followed by a few cases caused by platelet concentrates and plasma (Kroll et al., 1993). About 150–200 cases of PTP have been reported in the literature (McFarland, 2001). Typically, PTP is characterized by a sudden drop of platelet counts below values of 15 x 10^9 L^-1 leading to severe or even life-threatening bleeding complications without intervention. Preformed alloantibodies against platelet antigens, especially the HPA-1a-antigen, are detected in alloantigene-negative patients. In rare cases, platelet-reactive antibodies with specificities other than HPA-1a, e.g. HPA-3a or -5b, were described (von dem Borne et al., 1980; Kroll et al., 1993; Lubenow et al., 2000). Additional HLA class I antibodies are not unusual. Most patients are multiparous women of middle or higher age with a history of immunization by pregnancy or transfusion. We report on a PTP case of a woman who received two units of leucocyte-reduced RBC and developed severe thrombocytopenia 6 days later, accompanied by alloreactive and autoreactive platelet antibodies.

CLINICAL SITUATION

A 46-year-old woman was admitted to the hospital with acute progressive kidney insufficiency and anaemia (Hb 8.4 g dL^-1). She suffered from a progressive carcinoma of the urinary bladder and from coronary heart disease after myocardial infarction. The patient had one child; no information was available on preceding transfusions. She received two units of leucocyte-reduced packed RBCs within 2 days resulting in an haemoglobin value of 10.7 g dL^-1 on day 4 (for follow-up, see Fig. 1). On day 7, her platelet count fell from initially 365–429 x 10^9 L^-1 to 189 x 10^9 L^-1 and 1 day later suddenly dropped to 4 x 10^9 L^-1. Thrombocytopenia was accompanied by
macrohaematuria, petechiae and bleeding of the ear. There was no evidence for sepsis. Because she was treated with heparin, heparin-induced thrombocytopения (HIT) was supposed first and heparin was omitted, but this was without effect. On day 9, four unselected platelet concentrates were applied without any benefit. Four RBC concentrates were applied during the next 3 days without HPA-1a or HLA selection. After detection of HPA-1a and HLA class I antibodies without a clear serological sign of HIT, she was treated beginning from day 12 for 5 days with ivIgG (5 g d⁻¹; Octagam, Octapharma, Langenfeld, Germany). Platelet counts began to normalize on day 16 and remained stable between 204 and 479 × 10⁹ L⁻¹. The underlying disease of the patient was treated by cystectomy on day 45, and she obtained four units of HPA-1a-negative and HLA-class I-compatible (cross-match negative) packed RBC. Platelet counts temporarily fell from 428 × 10⁹ L⁻¹ to 240 × 10⁹ L⁻¹ but recovered within 4 days to values above 300 without further treatment. She was discharged on day 60 with 585 × 10⁹ platelets L⁻¹.

**PLATELET SEROLOGY**

The patient’s blood groups were determined as A, CCD.ee, kk. No irregular blood group antibodies were detected.

The platelet antigen genotype was determined by PCR with allele-specific primers (PCR-ASP) (Lubenow et al., 2000) as HPA-1(a–, b+), HPA-2 (a+, b–), HPA-3(a–, b+) and HPA-5(a–, b+). Platelet serology was performed by the MAIPA assay (Kiefel et al., 1987) using monoclonal antibodies directed against the platelet glycoprotein complexes GPIIb/IIIa, GPIa/IIa, GPIb/GPIX and against β₂m (HLA class I). A platelet antibody, binding to the GPIIb/IIIa complex of HPA-1a-positive platelets, was observed on day 11, while HPA-1a-negative cells produced negative test results (Table 1). No IgG binding to GPIa/IIa, GPV and GPIb/IX was demonstrated. On the contrary, serum from day 13 was not only strongly positive in the MAIPA assay with GPIIb/IIIa on HPA-1a homozygous platelets but also exhibited IgG reactivity with GPIa/IIa on HPA-5a- and on HPA-5b-homozygous platelets.

**Table 1.** HPA antibody detection during the course of the disease

<table>
<thead>
<tr>
<th>Day</th>
<th>HPA-1a/la</th>
<th>GPIa/IIa</th>
<th>HPA-1a/la</th>
<th>GPIa/IIa</th>
<th>HPA-1a/la</th>
<th>GPIa/IIa</th>
<th>HPA-1a/la</th>
<th>GPIa/IIa</th>
<th>HPA-1a/la</th>
<th>GPIa/IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>+++</td>
<td>-</td>
<td>+++*</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>nt</td>
<td>nt</td>
<td>+++</td>
<td>-</td>
<td>nt</td>
<td>nt</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>31</td>
<td>258</td>
<td>286</td>
<td>585 on day 60</td>
<td></td>
<td></td>
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*Additional weak reactivity with GPIIb/IIIa on HPA-1bb, -3aa platelets.

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cells. Weak reactivity was observed with GPIIb/IIIa on HPA-1(a–, b+), −3(a+, b–) platelets. The HPA-1a alloantibody persisted on day 61, whereas GPIIa/IIIa reactivity was no longer detectable in the MAIPA assay. In addition to the MAIPA, HPA antibody detection was performed by a commercial glycoprotein-specific ELISA assay (PAK12; GTI, Brookfield, WI, USA) on patient serum drawn on days 13, 47 and 63 (Table 1). The patient serum was positive with GPIIIa preparations of HPA-1(a+, b–) cells but negative with HPA-1(a–, b+) cells. There was no binding to GPIIa/IIa or GPIb/IX at any time, in contrast to the results obtained with the MAIPA assay.

Detection of platelet-associated IgG unfortunately was not possible due to the shortage of material. Besides the HPA-1a antibody, HLA class I antibodies with strong reactivity against HLA-B7, -27, -13, 37, -55, -56, -57, -60 and -61 were detected. The patient was positive for the DRB3* gene (serological DR52).

Drug-induced (Furosemid, Xylitol, Enalapril, Metamizol and Tramadol) antibodies, detected in an ELISA assay with complete platelets, could not be excluded, because of disturbing HLA-antibodies, but were regarded as less probable because of the clinical picture and other test results.

Diagnosis of HIT by detection of platelet factor 4 (PF4)/heparin-specific antibody was performed by the HIPA assay (Eichler et al., 1999) and by ELISA (Eichler et al., 2002). The HIPA assay was negative, while the ELISA produced positive results which can result from disturbing HLA antibodies. These results are not typical for HIT but do not exclude this diagnosis.

DISCUSSION

The case of post-PTP presented here may corroborate the theory of autoantibody formation in addition to preformed alloantibody as inducing agent for platelet destruction. Following the typical picture of PTP, a middle-aged woman with one child developed strong thrombocytopenia with platelet counts of $4 \times 10^9 \text{ L}^{-1}$ 7–8 days after transfusion of two units of packed RBC. Besides a strong HPA-1a alloantibody (the patient was negative for HPA-1a), additional serum reactivity with GPIIa/IIa on both HPA-5a- and HPA-5b-positive platelets and weak reactivity with HPA-1b/1b platelets was demonstrated during the acute phase of the disease. This finding fits to the hypothesis that autoantibodies developing after transfusion of incompatible platelet antigen in addition to preformed alloantibodies are responsible for massive platelet destruction in PTP (Morrison & Mollison, 1966; Taaning & Tonnesen, 1999). Alternatively, immune complexes of soluble platelet donor antigen and patient platelet antibody can bind to autologous patient platelets through a high-affinity Fc-receptor-mediated attachment, thus causing platelet destruction (Shulman et al., 1961). As a third possibility, soluble donor platelet antigens can bind to the patients’ platelets, converting these from antigen-negative to antigen-positive and leading to destruction through patient alloantibody (Kickler et al., 1986). Increased levels of IgG on patient’s platelets have been demonstrated as well as eluted antibodies with strong reactivity against HPA-1a-positive platelets and weak reactivity against HPA-1a-negative autologous platelets (Pegels et al., 1981), but platelet antigen-antibody complexes have not been demonstrated in the serum of PTP patients (McFarland, 2001). The GPIIa/IIa-reactive IgG antibody of our patient was exclusively detected in the MAIPA assay and, in contrast to the persisting HPA-1a reactivity, vanished when the patient’s platelet counts had recovered. Previously, autoantibodies of the IgM type were discussed (Berney et al., 1985) as well as IgG and IgM autoantibodies in addition to HPA-1a alloantibodies (Taaning & Tonnesen, 1999). Unfortunately, no information was available on platelet-associated IgG as well on subclass restriction of the detected antibodies.

The rapid diagnosis of PTP and exclusion of HIT followed by application of ivIgG brought the platelet counts to normal values within 4 days, while recovery without intervention is reported to last between 1 week and 2 months (Mueller-Eckhardt et al., 1980; McFarland, 2001). IvIgG was applied over 5 days in low doses (5 g day$^{-1}$), although high-dose therapy with 1 mL kg$^{-1}$ body weight (bw) over 2 days or 0.4 g kg$^{-1}$ bw over 5 days is reported as standard (Mueller-Eckhardt et al., 1983; Berney et al., 1985; Kroll et al., 1993). But nevertheless, in this case, lower doses of ivIgG also were successful.

When the patient later on was in need for platelet substitution because of surgical intervention, she received four RBC units from HPA-1a-negative donors. Platelet counts slightly dropped but increased to values above $300 \times 10^9 \text{ L}^{-1}$ within 4 days, showing that blood transfusion from antigen-negative donors is successful after PTP. Thus, early recognition and clear differential diagnosis can prevent a harmful outcome of PTP.

REFERENCES


