



# Immune hemolytic anemia—selected topics

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Autoimmune hemolytic anemia (AIHA) is most often idiopathic. However, in recent years, AIHA has been noted with increased incidence in patients receiving purine nucleoside analogues for hematologic malignancies; it has also been described as a complication of blood transfusion in patients who have also had alloimmunization. As the technology of hematopoietic stem cell transplantation has become more widespread, immune hemolysis in the recipients of ABO-mismatched products has become better recognized. The syndrome is caused by passenger lymphocytes transferred from the donor and, although transient, can be quite severe. A similar syndrome has been observed in recipients of solid organ transplants when there is ABO-incompatibility between donor and recipient.

Venous thromboembolism is a little-recognized, though likely common, complication of AIHA, and may in some instances be related to coexistent antiphospholipid antibodies. While AIHA is a well-documented complication of malignant lymphoproliferative disorders, lymphoproliferative disorders may also paradoxically appear as a consequence of AIHA.

A number of newer options are available for treatment of AIHA in patients refractory to corticosteroids and splenectomy. Newer immunosuppressives such as mycophenolate mofetil may have a role in such cases. Considerable experience has been accumulating in the last few years with monoclonal antibody therapy, mainly rituximab, in difficult AIHA cases; it appears to be a safe and effective option.

## Unusual Aspects of the Epidemiology of AIHA

### *Association with Therapy with Purine Nucleoside Analogues*

**B**ecause of the association of autoimmune hemolytic anemia (AIHA) with chronic lymphocytic leukemia, many people with AIHA can be expected to have been treated with purine nucleoside analogues such as fludarabine and cladribine. In 1995, Myint et al reported on 52 patients with AIHA treated with fludarabine, in whom severe AIHA occurred in 12 (21%) after a median of 4 courses. Nine of these 12 had no prior evidence of AIHA. Eight were retreated with fludarabine at a later time, and severe AIHA recurred in 6.<sup>1</sup> The authors opined that a disturbance of immunoregulatory T cells was responsible for the problem, in that T-cell lymphopenia is a recognized effect of fludarabine. Weiss et al reviewed this subject, and reported on 24 patients with AIHA following fludarabine therapy for chronic lymphocytic leukemia.<sup>2</sup> Most of the patients developed the AIHA after 1 to 3 courses of drug, and 7 (29%) died of complications related to the AIHA. Of 8 patients rechallenged with fludarabine at a later time, 7 had recurrent AIHA, and 3 died. The authors propose as a

mechanism the release of a suppressed autoantibody to a native erythrocyte antigen.

This problem has also been reported after the use of cladribine. Fleischman and Croy reported on a patient with severe AIHA that developed a few weeks after treatment of chronic lymphocytic leukemia with cladribine.<sup>3</sup> More recently, Aslan reported a case of a patient with Waldenström macroglobulinemia who developed warm antibody AIHA a few months after therapy with cladribine.<sup>4</sup> The authors bolster the causative assumption by noting that cold-mediated IgM antibody is more likely to occur in macroglobulinemia, rather than a warm antibody. Byrd et al noted a case of fludarabine-associated AIHA that recurred fatally upon treatment with pentostatin.<sup>5</sup>

Recent studies have suggested that the combination of fludarabine plus cyclophosphamide, or that combination plus rituximab, may protect against the development of AIHA in patients with chronic lymphocytic leukemia. Dearden et al noted a much lower rate of DAT positivity after treatment with fludarabine/cyclophosphamide than after fludarabine alone.<sup>6</sup> Borthakur et al noted a similar incidence of hemolytic anemia in patients treated with fludarabine/cyclophosphamide/rituximab to that in histori-

cal controls, and even lower if only DAT-positive patients were considered.<sup>7</sup>

Clinicians need to be aware of the risk that use of purine nucleoside analogues in treating malignant lymphoproliferative disorders may induce AIHA, and that this may be severe or even fatal at times. There may be a role for rituximab in the treatment of such episodes.<sup>8</sup>

### *Association with Blood Transfusion*

While alloantibody formation is a recognized and reasonably common complication of blood transfusion, the possibility of autoantibody formation has not been well recognized. Young et al analyzed over 2600 patients with a positive direct antiglobulin test or indirect antiglobulin test, and identified 41 patients who had both an autoantibody and an alloantibody. About a third of them developed their autoantibody in close temporal association with alloimmunization following recent transfusion.<sup>9</sup> Therefore, AIHA developed either concurrently or shortly after alloimmunization from blood transfusion. The authors conclude that AIHA is a potential complication of allogeneic red blood cell transfusions and recommended supportive treatment with iron and erythropoietin analogues, avoiding further transfusion whenever possible. This complication of red blood cell transfusion may be more common than previously appreciated.<sup>10</sup> It has also been noted in patients with hemoglobinopathies who have received multiple transfusions.<sup>11-13</sup> For example, Aygun et al noted an incidence of 8% warm autoantibody development in children and nearly 10% in adults with sickle cell disease who had received transfusions.<sup>11</sup> Petz has summarized the sickle cell hemolytic transfusion reaction syndrome, in which patients develop more severe anemia after a transfusion reaction than they had before the transfusion, indicating that native RBC are also being lysed. There is the development of a positive DAT and frequent association with symptoms of a pain crisis.<sup>14</sup> Petz cites this as an example of “bystander hemolysis,” in which autoimmune hemolysis occurs after exposure to alloantigens; that is, there is hemolysis of cells that do not carry the antigen against which the antibody is directed.<sup>14,15</sup>

### *Association of Immune Hemolysis with Allogeneic Hematopoietic Cell Transplantation*

Immune hemolysis may be a complication of hematopoietic stem cell transplantation when there is a minor ABO blood group incompatibility between the donor and recipient, defined as the donor having lymphocytes capable of producing antibodies against recipient RBC antigens. It occurs most often when the donor is group O and the patient group A, and may occur in up to 10% to 15% of patients.<sup>16,17</sup> Presumably donor-derived isohemagglutinins

directed against recipient RBC lead to hemolysis. The resultant hemolysis begins within the first 2 weeks after infusion, and may be abrupt in onset and severe, sometimes with accompanying intravascular hemolysis and renal failure.<sup>18</sup>

The problem has been attributed to the “passenger lymphocyte syndrome,” caused by production of antibody by rapidly proliferating passively transferred lymphocytes transfused with the stem cell product. Passive transfer of antibody in plasma accompanying the product does not appear to be important, as the hemolysis does not occur immediately. The antibody production and subsequent hemolysis occur while the patient is still pancytopenic from the conditioning regimen, before immune reconstitution occurs. It is thought to be related to the fact that IgG-type anti-A and anti-B are more common in group O persons than in group A and B persons. Hemolysis may also be a result of anti-D, anti-E, anti-s, anti-Jk<sup>b</sup> and anti-Jk<sup>a</sup>.<sup>19</sup> The hemolysis lasts 5 to 10 days and gradually subsides as the recipient’s residual incompatible red cells are lysed and replaced by transfused group O cells, or by red cells of donor type produced by engrafting stem cells. Later, antibody production by passenger lymphocytes that do not engraft dissipates.

Several factors appear to predispose to passenger lymphocyte syndrome: use of cyclosporine alone without methotrexate for graft-versus-host disease prophylaxis; use of peripheral blood stem cell product rather than bone marrow; use of reduced-intensity preparative regimens; use of a non-genotypically HLA-matched donor; and possibly, use of a female donor. The problem has not been noted with umbilical cord blood stem cell transplantation.

Patients develop rapid onset of hemolysis, associated with a positive direct antiglobulin test and the presence of anti-A or anti-B antibodies in their serum. Evidence of intravascular hemolysis with accompanying hemoglobinuria and renal failure may ensue.

Management strategies include reduction of the plasma volume of stem cell product to reduce the amount of anti-A and anti-B infused. While passive transfer of antibody is not thought to be the main problem, large volumes of anti-A or anti-B in donor plasma can sometimes cause hemolysis and should be avoided as well. Red cell transfusions should be with compatible cells or group O cells (if patient is type AB, and donor is type A or B, donor cells may be used). Corticosteroids are commonly used. Platelet transfusions and other plasma-containing products should be of recipient type, to minimize infusing anti-A and anti-B, and renal function should be assured. If significant hemolysis occurs,

exchange transfusion may be required to replace the patient's antigen-positive red blood cells with group O red blood cells. Prophylactic red blood cell exchange transfusion has been proposed in some cases.<sup>20</sup>

When there is a major ABO-incompatibility, defined as when the recipient has preformed antibody to donor RBC antigens, such as when the donor is type A or type B and the recipient type O, hemolysis may be prevented by removing red cells from the donor product. Persistence of recipient ABO antibodies may lead to persistent hemolysis for a few months, and patients may need to be supported with transfusion of type O blood. Recommendations for blood product support in minor and major ABO-mismatched hematopoietic stem cell transplantation have been reviewed in detail by Petz.<sup>18</sup>

In some reported instances of hemolytic anemia post-hematopoietic stem cell transplantation, the degree of hemolysis exceeded the total erythrocyte volume of the recipient, suggesting that transfused group O cells, in addition to the recipient's native cells, were also being lysed—another example of the phenomenon of “bystander” hemolysis.<sup>14,21</sup>

Autoimmune hemolytic anemia has also been reported following hematopoietic stem cell transplantation. This is thought to be due to antibody being produced by the donor immune system against antigens on red cells of donor origin, hence AIHA. In a number of cases studied, no evidence of residual recipient cells was found, leading to the conclusion that the cause was an autoimmune reaction of the graft against its own product. A report in a pediatric population noted an incidence of 6%, with a median time of onset of 4 months after transplant; mortality was quite high, perhaps worsened by the additional immunosuppressive therapy required to manage the AIHA.<sup>22</sup> It was more common when transplant was performed for metabolic diseases than for malignant disorders. It was also reported to occur in 5% of 6-month survivors of T cell-depleted transplants<sup>23</sup> in one report, and in 9 (3%) of a group of 293 transplanted patients.<sup>24</sup> In the latter study, 5 patients had warm antibody AIHA, and 4 had cold agglutinin disease. Patients with warm AIHA developed it later, between 6 and 18 months, versus 2 to 8 months for those with cold agglutinins. Additional reports have included several cases following cord blood transplants, with resultant AIHA and Evans syndrome.<sup>25,26</sup> There have been reports of successful therapy of AIHA following hematopoietic stem cell transplantation with rituximab.<sup>27,28</sup>

### *Association of Immune Hemolysis with Orthotopic Solid Organ Transplantation*

Immune hemolysis has also been associated with solid organ transplantation.<sup>29-31</sup> This is thought also to relate to passenger lymphocyte syndrome and involves mainly group O donors, though a few have been in AB recipients with non-AB donors. The risk and degree of hemolysis is in proportion to the mass of lymphocytes transplanted—lowest in kidney (antibody in 17%, hemolysis in 9%), next higher in liver (antibody in 40%, hemolysis in 29%), and highest in heart-lung transplants (antibody in 70%, hemolysis in 70%). The hemolysis is of rapid onset, with a positive direct antiglobulin test and detectable serum antibody against A or B or both. Antibody against D antigen has also been reported.<sup>32-34</sup> Onset is between 3 and 24 days. In one study of 43 patients, 36 had IgG antibody, 35 had C3, and 28 had both.<sup>29</sup> The average transfusion requirement was 6.5 units. In contrast to hematopoietic cell transplants, where the patient's red blood cells eventually become replaced by donor marrow-produced ones, patients with solid organ transplants continue to make red cells that are incompatible with the transplanted organ. However, hemolysis is generally transient, since the lymphocytes transferred with the donor organ do not proliferate indefinitely and do not engraft.

Management of hemolysis in solid organ transplant patients includes transfusion of group O red cells, avoidance of ABO-incompatible plasma products, and maintenance of adequate renal function. Sometimes red blood cell exchange is necessary to decrease the volume of incompatible cells that can be targets for hemolysis. Transfused red cells should be ABO-identical, or compatible with recipient serum, irrespective of donor organ type. If the donor and recipient have different blood type, products should be used that are ABO-compatible with both the recipient and donor red cells, as well as the donor organ tissue type, to avoid transfusing antibody that may contribute to hemolysis.

The characteristics and management of immune hemolysis following transplantation of ABO-mismatched hematopoietic stem cells and solid organs has been reviewed recently.<sup>35</sup> Guidelines for blood product selection in patient with ABO-mismatched solid organ transplants are offered by Petz.<sup>18</sup>

### **Complications of AIHA**

#### *Thromboembolism*

In an early review of AIHA, the most common cause of death was pulmonary embolism (4 of 47 patients).<sup>36</sup> All of these patients had had a splenectomy, and all were receiving corticosteroid therapy. In a more recent review by Pullarkat et al, 8 of 30 patients (27%) suffered from an

episode of venous thromboembolism.<sup>37</sup> A total of 9 had a detectable lupus anticoagulant and 17 had anticardiolipin antibodies detected. Among the 8 with thrombosis, 5 had a lupus anticoagulant, and 4 had anticardiolipin antibodies. The authors attributed the thrombosis to disruption and loss of red cell membranes resulting in exposure of phosphatidyl serine, and a subsequent surface for formation of tenase and prothrombinase complexes. Other factors implicated in the thrombotic tendency in patients with AIHA included cytokine-induced expression of monocyte or endothelial tissue factors. The authors postulated that the detection of a lupus anticoagulant identifies patients with AIHA at particularly high risk for venous thromboembolism, and suggested that serious consideration be given to prophylactic anticoagulation in such patients. However, they point out that thrombosis also occurred in 15% of AIHA patients who did not have a lupus anticoagulant, so other factors are likely at work.

Kokori et al, in a review of AIHA in patients with systemic lupus erythematosus, found the risk of thrombosis to be increased more than 4-fold, particularly in the presence of IgG anticardiolipin antibody.<sup>38</sup>

Hendrick has reviewed this issue more recently and concluded that patients with AIHA are indeed at high risk for thromboembolism. In an audit of 23 patients with warm antibody AIHA and 5 with cold agglutinin hemolysis, venous thromboembolism was noted in 6 cases, 4 of which were fatal. These patients did not have detectable antiphospholipid antibodies. In an analysis of 36 hemolytic episodes, venous thromboembolism occurred in 5 of 15 without anticoagulant prophylaxis, but only in 1 of 21 in which prophylaxis was used.<sup>39</sup>

Although it is premature to recommend anticoagulant prophylaxis in general for patients with hemolytic episodes from AIHA, consideration might be given to those at particularly high risk, such as those with evidence of coexisting antiphospholipid antibodies.

### *Lymphoproliferative Disorders*

Patients with lymphoproliferative disorders are well known to have a higher risk for development of AIHA; this is particularly true of chronic lymphocytic leukemia. Interestingly, there may also be an increased risk for future development of lymphoproliferative disorders in patients with AIHA. Sallah et al reported on 107 patients with AIHA, of whom 67 had idiopathic AIHA, and 40 had an associated immune disorder (eg, rheumatoid arthritis, temporal arteritis, Crohn's disease, lupus, thyroiditis, Sjogren's syndrome). Nineteen of the 107 (18%) subsequently developed a malignant lymphoproliferative disorder, at a

median of 26 months after onset of the AIHA.<sup>40</sup> Risk factors for development of such a disorder were age, the presence of an underlying autoimmune disease, and a coexistent serum gammopathy. None of the patients had underlying HIV infection. The authors postulate that the development of a malignant lymphoid disorder is likely a multistep process, with an earlier proliferative phase involving chronic antigenic stimulation prior to a mutation leading to malignant change.

This association is being recognized with greater frequency. In a study of 4 million men at VA Hospitals, Landgren et al noted a nearly 4-fold increased risk of chronic lymphocytic leukemia in patients with AIHA, with a latency period of at least 5 years.<sup>41</sup> They acknowledged the possibility that an undetected early-stage leukemic condition might have been undetected in some of the patients. The same group, in a later analysis, found increases in T-cell lymphoma and marginal zone lymphoma.<sup>42</sup> In a pooled analysis, Ekstrom Smedby found a 2- to 3-fold increase in B-cell non-Hodgkin lymphomas, especially diffuse large cell lymphoma, in patients with long-duration AIHA.<sup>43</sup> Finally, there has also been noted an increase in myeloid malignancies in patients with AIHA.<sup>44</sup>

### **Therapy of Refractory Cases of AIHA**

The standard therapeutic approaches to treatment of AIHA include corticosteroids, splenectomy and immunosuppressive drugs. In the past several years, certain newer therapies have become available and have shown evidence of success. These are primarily used in patients who are not candidates for or fail to respond to splenectomy, those who relapse after splenectomy, and those who cannot maintain stable hemoglobin levels without unacceptably high doses of corticosteroids.

#### *Intravenous Immune Globulin (IVIg)*

Flores et al reviewed the cases of 73 patients treated with IVIg and found responses in 29 (40%).<sup>45</sup> Children were more likely to respond, as were patients with initial hepatomegaly and lower initial hemoglobin levels.

#### *Danazol*

Danazol, which has been used more in refractory cases of immune thrombocytopenia, has also been used in AIHA. Ahn reported good to excellent results in the majority of patients treated.<sup>46</sup> In another series of 17 patients treated with the combination of prednisone and danazol, excellent responses were noted in 80% of those who received the combination as first-line therapy; treatment was less effective in patients who had relapsed and in those with Evans' syndrome.<sup>47</sup>

### *Newer Immunosuppressives*

Howard et al reported on the use of mycophenolate mofetil in 4 patients with refractory AIHA.<sup>48</sup> Patients were treated with 500 mg per day initially, then 1000 mg per day. All 4 had a complete or good response. Another study from France in patients with refractory immune cytopenias showed excellent results with this drug.<sup>49</sup>

### *Monoclonal Antibodies*

There has been considerable interest in using the monoclonal antibodies now routinely employed in the treatment of B-cell lymphoid neoplasms, namely rituximab and, to a lesser extent, alemtuzumab, in patients with AIHA. Zecca first reported on a child with pure red cell aplasia and AIHA treated successfully with rituximab and IVIG.<sup>50</sup> Shanafelt reported on 5 patients, 2 of whom had a complete response. In an additional 4 patients with Evans' syndrome, complete responses occurred in either the immune thrombocytopenia or the AIHA, but not both.<sup>51</sup> Ramanathan noted 2 patients with refractory disease who demonstrated prolonged remissions with rituximab.<sup>52</sup>

Two groups have reported on the use of rituximab in patients with AIHA in the setting of chronic lymphocytic leukemia. Gupta reported on the combined use of rituximab, cyclophosphamide and dexamethasone in 8 patients with refractory AIHA; the results were excellent, including in relapsed patients, with 5 patients converting to negative DAT status.<sup>53</sup> D'Arena et al noted high response rates with rituximab in 14 patients, only one of whom had fludarabine-associated AIHA.<sup>54</sup>

There has been only limited experience with alemtuzumab in AIHA, with one report noting responses in 3 of 4 patients treated, and one showing all of 5 patients treated with good responses.<sup>55,56</sup>

The role of monoclonal antibodies in the therapy of autoimmune cytopenias has been reviewed in detail recently.<sup>57</sup>

It is reasonable to conclude that monoclonal antibody therapy, specifically rituximab, is a safe and effective therapy for refractory AIHA. It is likely that as our experience with the drug evolves, it will be used at an earlier point in therapy, before more toxic immunosuppressives, and in lieu of splenectomy in some cases.

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### **Disclosures**

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Off-label drug use: Use of rituximab, danazol and mycophenolate in refractory cases of autoimmune hemolytic anemia.

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