Autoimmune Hemolytic Anemia in Chronic Myeloid Leukemia

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**Abstract**

**Background:** Autoimmune hemolytic anemia (AIHA) might be associated with underlying hematological malignancies such as chronic lymphocytic leukemia. However, the association between AIHA and chronic myelogenous leukemia is extremely unusual. **Summary:** We reviewed case reports and series of 54 patients with chronic myeloid leukemia (CML) who developed autoimmune hemolysis between 1952 and 2018. Almost all the patients were in the chronic phase and were classified into transplant and non-transplant groups. The onset of autoimmune hemolysis was earlier in the transplant group and required second- and third-line therapy to control it. The etiology of hemolysis is poorly understood but attributed in the transplant group to immune reconstitution, viral infections, or CML relapse. On the other hand, it is thought to be related in the non-transplant group to CML medications, especially interferon. **Key Messages:** Although AIHA is uncommon in chronic myelogenous leukemia patients, it should be in the differential diagnosis list for those who develop a sudden drop in hemoglobin without a bleeding source.

**Introduction**

Autoimmune hemolytic anemia (AIHA) is an unregulated immune reaction toward a patient’s own RBC surface antigens, leading to extravascular hemolysis in warm AIHA mediated mainly by IgG, and intravascular hemolysis in cold agglutinin disease mediated by IgM. Diagnosis of AIHA is suggested by the evidence of hemolysis on anemia workup and is confirmed by a positive direct antiglobulin (Coombs) test [1]. Treatment efforts are directed to counteract hemolysis or to increase RBC survival in addition to ruling out and managing possible associated conditions [2].

Warm autoimmune hemolytic anemia is idiopathic in around half of the patients. However, it is known to be linked in the rest with autoimmune disorders, viral infections, drugs, or cancers [1]. Both solid and hematological malignancies can be associated with AIHA, but the latter is far more frequent [3]. The most well-recognized underlying hematological malignancies are lymphoproliferative disorders, especially chronic lymphocytic leukemia (CLL) in which AIHA can be diagnosed prior to, coexist, or develop during the treatment of CLL [4].

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by uncontrolled proliferation of myeloid precursor cells. Majority of the patients have translocation between chromosomes 9 and 22.
AIHA and CML

(t(9;22), forming Philadelphia chromosome which results in the production of BCR-ABL1 protein with high tyrosine kinase activity that enhances cell division. CML can manifest in any of its three phases: chronic, accelerated, and blast crisis. However, most of the patients are diagnosed in the chronic phase and treated with tyrosine kinase inhibitors with very good prognosis [5].

The combination of CML and AIHA, in contrast to CLL, is extremely unusual as few case reports and series have been published in the medical literature linking both entities. In this review, we are going to shed light on what is known so far about this association, patients’ characteristics, and how AIHA was treated in such cases and analyze the possible underlying etiology behind it in CML patients.

Methodology

We searched the medical literature through PubMed and Google Scholar using the following terms: chronic myeloid leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, CML, autoimmune hemolytic anemia, autoimmune hemolysis, and AIHA. Search-related English publications of case reports and series, which reported AIHA in adult CML patients from inception till May 2019, were screened by reading the title and the available abstract. Information regarding patients’ age, gender, CML phase, and treatment in addition to the onset of AIHA, its severity, therapy, and outcome were extracted from these articles and are summarized in Tables 1–3. Cases of alloimmune-mediated hemolysis after hematopoietic stem cell transplantation (HSCT) were not included if there was no concomitant autoantibody formation.

Results

To the best of our knowledge, 54 CML patients developed AIHA and were reported in 26 case reports and series [6–31] between 1952 and 2018. There was an almost equal distribution between male and female patients, with a median age of 41 years (ranging from 15 to 84 years). All of them were in the chronic phase of CML except 3 patients: 1 was in the accelerated phase and 2 were in blast crisis. Different lines of therapy were used for CML, reflecting the progress in its management over time: among the 54 patients, 1 was treated with focused radiotherapy to the spleen, 3 were treated with busulfan, 14 were treated with interferon alpha alone, 4 were managed with imatinib, and 31 underwent allogeneic HSCT (18 from bone marrow, 7 from umbilical cord blood, 1 from peripheral blood, and 5 were not specified). Almost half of the transplantation was from matched unrelated donors. Different medications were used for conditioning, including cyclophosphamide, busulfan, alemtuzumab, fludarabine, and anti-thymocyte globulin. All transplanted patients received cyclosporin with or without methotrexate for graft versus host disease prophylaxis.

Warm AIHA was confirmed with a positive direct antiglobulin test in 40 patients, whereas cold agglutinin disease was confirmed by cold agglutinin antibodies in 7 patients, and both types were diagnosed simultaneously in 4 patients. Full article was not available in 3 publications to determine whether AIHA was of warm or cold type. The onset of AIHA was variable, with a median of 19 months after CML treatment (ranging between 3 months and 15 years) in patients who did not undergo HSCT, with an exception of 1 patient who developed autoimmune hemolysis 4 years prior to CML diagnosis. On the other hand, the onset of AIHA in the transplant group was earlier, with a median of 6.5 months (ranging from 8 days till 19 months posttransplantation). Hemoglobin (Hb) level at the time of diagnosis of AIHA was also different among patients, with a median level of 5.9 g/dL (the lowest reported value was 3.4 g/dL and the highest reading was 8 g/dL).

Autoimmune workup, viral serology, or both were done as part of the investigations in 12 publications [8, 15–17, 20–26, 28, 31]. It was noteworthy that almost half of the transplant patients had developed viral infections prior to the diagnosis of AIHA with variable onset (12 cases due to Cytomegalovirus, 2 cases due to varicella zoster virus, 1 case due to parvovirus, and 1 due to influenza virus). Blood transfusion was reported before developing hemolysis in 3 cases, 2 of them from the transplanted group. From the bone marrow-transplanted group, 9 of 18 cases were diagnosed with AIHA at the same time of CML relapse.

AIHA was treated in 35 cases with steroids, mainly prednisone, with different doses and duration. However, some of them required second- and third-line treatment with splenectomy (8 patients), intravenous immunoglobulin (16 patients, all of them from the transplanted group), rituximab (4 patients), bortezomib (1 patient), and plasmapheresis (2 patients), in addition to donor lymphocyte infusion in 5 patients who underwent bone marrow transplantation. Treatment was not specified in 13 patients. Hb level after AIHA management was underreported. However, more than half of all cases showed improvement with treatment. On the other hand, 14 patients, most of them from the transplanted group, died due to different reasons (sepsis, pneumonitis, hemolysis, blast crisis, graft versus host disease, liver failure, and intracranial hemorrhage).
| 1st author       | Year of publication | Age, years/ gender | CML phase | CML therapy | AIHA onset | Hb, g/dL | AIHA therapy | Duration of therapy | Hb, g/dL – follow-up | Outcome                      |
|------------------|---------------------|-------------------|-----------|-------------|------------|---------|---------------|---------------------|--------------------------|------------------------------|
| Osgood E. [6]    | 1952                | N/A               | Chronic   | N/A         | N/A        | N/A     | N/A           | N/A                 | N/A                      | N/A                         |
| Vidbaek A. [7]   | 1962                | 70/F              | Chronic   | N/A         | 12 mo      | 6.4     | Prednisone 40 mg | 2 wk                | N/A                      | Died with aspergillus sepsis |
|                  |                     | 48/F              | Radiotherapy | 9 mo (both after CML diagnosis) | 3.4 | Prednisone 40 mg | 1 wk                | N/A                      | Died with blast crisis after 3 mo |
| Maklonado N.I. [8] | 1967            | 84/M              | Chronic   | Busulfan intermittent use | 12 mo (after CML diagnosis) | 7 | Prednisone 50 mg | 1 mo (tapered) | 8.9 | Died with pneumonia after 1 mo |
| Cohen S.M [9]    | 1967                | 45/F              | Chronic   | Busulfan for 2 wk | 4 yr* | 5 | Prednisone 60 mg | 6 mo (tapered) | 13 | Improved            |
| Arbaie Y.M. [10] | 1990                | 55/M              | Chronic   | Busulfan intermittent use | 3 yr (after CML diagnosis) | 8 | Prednisone | 5 wk | 14 | Improved            |
| Kumpf T.R. [11]  | 1990                | 47/F              | Chronic   | Allogenic BMT | 19 mo (after BMT) | N/A | Steroids | N/A | N/A | Improved            |
| Tamura T. [12]   | 1994                | 36/M              | Chronic   | Allogenic BMT | CAD 3 wk (after BMT) | N/A | Prednisolone | N/A | N/A | Improved            |
| Sacchi S. [13]   | 1995                | 7 patients: (42 (median) / 6 F, 1 M) | Chronic | IFN-α-2a IFN-α-2b for 14 mo (median) | 10 mo (median after CML diagnosis) | 7.6 (mean) | Prednisone (3 patients) Spleenectomy (1 patient) | N/A | N/A | Improved            |
| Andriani A. [14] | 1996                | 59/F              | Chronic   | IFN-α-2b for 27 mo IFN-α-2a for 38 mo | N/A | 7.7 | Prednisone (0.5–1 mg/kg) | 1–3 mo | N/A | Improved            |
| Chen F.E. [15]   | 1997                | 36/M              | Chronic   | Allogenic BMT | (12, 8, 7, 2, 2) mo (Post-BMT) | N/A | Prednisolone (4 patients) IVIg (3 patients) Spleenectomy + vincristine (1 patient) No treatment (1 patient) | N/A | N/A | Improved (3 patients) CML relapse (3 patients) Died (3 patients) with pneumonitis/thromboembolisms/GVHD |
| Stavroyianni N. [16] | 2001            | 27/M              | Chronic   | IFN-α-2b and hydroxyurea | 2 yr (post-CML diagnosis) | 5.3 | Prednisone | 1 mo | N/A | Improved            |
| Cwynarski K. [17] | 2001             | 9 patients: (32 (median) / 6 M, 3 F) | Chronic | Allogenic BMT | 15 mo (median – post-BMT) | N/A | Prednisolone + IVIg (9 patients) Spleenectomy (4 patients) Donor lymphocyte infusion (5 patients) | Variable (1–10 mo) | N/A | Improved (6 patients) Died with pneumonitis (2 patients) |
| Köksal A. [18]   | 2002                | 41/F              | Chronic   | IFN-α | 5 yr (post-CML diagnosis) | 5.5 | Prednisone (1 mg/kg) | 1 mo | 9 | Died with ICH and pneumonia          |
| Tóthová E. [19]  | 2002                | 2 patients       | Chronic   | IFN-α | N/A | N/A | N/A | N/A | N/A | N/A |
| Steegmann J.L. [20] | 2003            | 37/M              | Chronic   | IFN-α-2a for 4 yr CAD (post-CML diagnosis) | N/A | N/A | N/A | N/A | N/A | N/A |
| 1st author       | Year of publication | Age, years/ gender | CML phase     | CML therapy  | AIHA onset | Hb, g/dL | AIHA therapy | Duration of therapy | Hb, g/dL – follow-up | Outcome                                      |
|------------------|---------------------|-------------------|---------------|--------------|------------|----------|--------------|---------------------|----------------------|-----------------------------------------------|
| Qazilbash M.H.   | 2005                | 21/F              | Chronic       | Allogenic HSCT | 3 mo post-SCT AIHA and CAD | N/A      | Methylprednisolone (1 mg/kg) IVIg (0.5 g/kg) for 4 d Plasmapheresis for 2 wk | –                    | N/A                  | Died with fulminant liver failure            |
| Sanz J. [22]     | 2007                | 22/M 52/F 42/F 38/M | Chronic       | UCBT (2 patients) BMT (2 patients) | 1, 5, 10, and 17 mo posttransplant 2 AIHA 2 CAD | N/A      | Not specified for CML cases | N/A                  | N/A                  | Not specified for CML cases                |
| Calixto R. [23]  | 2012                | 47/F              | Accelerated   | Allogenic PBSCT | 8 d post-PBCST | 5        | Methylprednisolone (2 mg/kg) | 2 mo (tapered) | N/A                  | Improved                                    |
| Sanz J. [24]     | 2014                | 4 patients: 33 (median)/ N/A | Chronic       | Allogenic UCBT | 7.6 mo (median posttransplant) 1 AIHA 3 CAD | N/A      | Not specified for CML cases | N/A                  | N/A                  | 2 patients died with sepsis                |
| Yang Z. [25]     | 2014                | 26/F              | Chronic       | Allogenic HSCT | 3.6 mo posttransplant | N/A      | Not specified for CML case | N/A                  | N/A                  | Not specified for CML case                |
| Wang M. [26]     | 2015                | 49/M 34/M         | Chronic       | Allogenic HSCT | 6 and 7 mo post-SCT | N/A      | Prednisolone Rituximab Cyclosporine Splenectomy IVIg | N/A                  | N/A                  | Improved                                    |

AIHA, autoimmune hemolytic anemia; BMT, bone marrow transplantation; CAD, cold agglutinin disease; GVHD, graft versus host disease; CML, chronic myeloid leukemia; d, day; Hb, hemoglobin; HSCT, hematopoietic stem cell transplantation; ICH, intracranial hemorrhage; IFN-α, interferon alpha; IVIg, intravenous immunoglobulin; F, female; M, male; mo, month; N/A, not available; PBSCT, peripheral blood stem cell transplantation; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor; UCBT, umbilical cord blood transplantation; wk, week; yr, year.

*The onset of AIHA was prior to CML. † Abstract only was available.
### Table 2. Case reports and case series of AIHA in CML patients (TKI was used as part of CML therapy)

| 1st author               | Year of publication | Age, years/ gender | CML phase | CML therapy                                      | AIHA onset | Hb, g/dL | AIHA therapy                                                                 | Duration of therapy | Hb, g/dL – follow-up | Outcome                  |
|--------------------------|---------------------|--------------------|-----------|--------------------------------------------------|------------|---------|--------------------------------------------------------------------------------|---------------------|------------------------|--------------------------|
| Novaretti M.C. [27]      | 2003                | 45/M               | Chronic   | Imatinib 400 mg for 6 mo, then 600 mg for 6 mo   | 11 years post-CML diagnosis, 8 mo post-imatinib | 5.9      | Prednisone (1 mg/kg)                                                          | 6 mo (tapered)       | 12.1                   | Improved                 |
| Rokicka M. [28]          | 2009                | 21/F               | Chronic   | IFN-α for 7 mo Imatinib for 3 mo Hydroxyurea for 2 yr, then UCBT | 6 mo Post-UCBT AIHA and CAD | N/A     | Methylprednisolone (2–5 mg/kg) IVIg (0.5 g/kg), rituximab (4 doses), mycophenolate Mofetil cyclophosphamide (750 mg/m^2/d), plasmapheresis (7 sessions), splenectomy | –                   | N/A                    | Died with hemolysis after 9.5 mo |
| Lewandowski K. [29]      | 2016                | 68/M               | Chronic   | IFN-α + cytosine arabinoside (3 yr), then imatinib (9 yr) | 9 yr post-imatinib | 5.8     | Prednisone (1 mg/kg)                                                          | N/A                 | N/A                    | Improved                 |
| Garg S. [30]             | 2018                | 43/F               | Blast crisis | Imatinib                                      | 15 yr post-CML diagnosis | 3.7     | Prednisolone                                                                 | N/A                 | N/A                    | Improved                 |
| Cao L. [31]              | 2018                | 46/F               | Blast crisis | Dasatinib, then allogenic HSCT twice         | 7.5 mo post-SCT | 6.1     | Prednisolone (2 mg/kg) IVIg (2 g/kg) Rituximab 375 mg/m^2 Bortezomib        | 4 Mo                 | 12                     | Improved                 |

AIHA, autoimmune hemolytic anemia; CML, chronic myeloid leukemia; d, day; Hb, hemoglobin; HSCT, hematopoietic stem cell transplantation; IFN-α, interferon alpha; IVIg, intravenous immunoglobulin; F, female; M, male; mo, month; N/A, not available; SCT, stem cell transplantation; UCBT, umbilical cord blood transplantation; wk, week; yr, year.
| 1st author          | Antibody (IgG, IgM) titers | Reticulocytes, % | LDH, U/L | Total bilirubin, mg/dL | Haptoglobin, mg/dL | Transfusion, units | Time from diagnosis till treatment | Time from CML diagnosis till transplantation | Transplantation type |
|---------------------|-----------------------------|-----------------|---------|------------------------|-----------------|------------------|-------------------------------|---------------------------------------------|----------------------|
| Osgood E. [6]       | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Vidbaek A. [7]      | N/A                         | 3.6–4.6         | N/A     | 1.5                   | N/A             | N/A              | Not clear                     | N/A                          | N/A                  |
| Maldonado N.I. [8]  | N/A 1:8 Cold agglutinin     | 24              | N/A     | 2 (1.5 indirect)      | N/A             | Unit of 500 mL   | Not clear                     | N/A                          | N/A                  |
| Cohen S.M. [9]      | N/A                         | 14              | N/A     | N/A                   | N/A             | N/A              | Not clear                     | N/A                          | N/A                  |
| Arbaie Y.M. [10]    | N/A                         | 10.6            | 375     | 1.1 (0.9 indirect)    | 4               | N/A              | Not clear                     | N/A                          | N/A                  |
| Klumpp T.R. [11]    | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Tamura T. [12]      | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Sacchi S. [13]      | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Andriani A. [14]    | N/A                         | N/A             | N/A     | 0.27                  | 6.23            | N/A              | N/A                           | N/A                          | N/A                  |
| Chen F.E. [15]      | N/A                         | N/A             | N/A     | 0.27                  | 6.23            | 4.27             | 0.2                           | N/A                           | 2 matched unrelated donor, 3 sibling donor |
| Stavroyianni N. [16]| N/A                         | 22.2            | 515     | 3.26 (2.7 indirect)   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Cwynarski K. [17]   | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | Not clear                     | Matched               |
| Köksal A. [18]      | N/A                         | 4.2             | 2,000   | 13                     | 5 units of 500 mL | N/A              | N/A                           | N/A                          | N/A                  |
| Tóthová E. [19]    | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Steegmann J.L. [20] | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | N/A                          | N/A                  |
| Qazilbash M.H. [21] | N/A                         | 1051            | 4.7     | N/A                   | N/A             | N/A              | 2 yr                          | Matched unrelated donor      |                      |
| Sanz J. [22]        | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | 2 matched unrelated 1 minor ABO mismatched 1 sibling donor |                      |
| Calixto R. [23]     | IgG 1:2                     | 791             | 7       | N/A                   | 6               | Directly         | N/A                           | Matched related donor Minor ABO incompatibility |                      |
| Sanz J. [24]        | N/A                         | N/A             | N/A     | N/A                   | N/A             | N/A              | N/A                           | Unrelated donors: 2 ABO matched 2 ABO minor mismatch |                      |
| 1st author         | Antibody (IgG, IgM) titers | Reticulocytes, % | LDH, U/L | Total bilirubin, mg/dL | Haptoglobin, mg/dL | Transfusion, units | Time from diagnosis till treatment | Time from CML diagnosis till transplantation | Transplantation type                      |
|-------------------|----------------------------|------------------|----------|------------------------|--------------------|-------------------|-----------------------------------|---------------------------------------------|--------------------------------------------|
| Yang Z. [25]      | N/A                        | N/A              | N/A      | N/A                    | N/A                | N/A               | N/A                               | N/A                                         | Unrelated donor                           |
| Wang M. [26]      | N/A                        | N/A              | N/A      | N/A                    | N/A                | N/A               | N/A                               | N/A                                         | 2 unrelated donors                         |
| Novaretti M.C. [27]| N/A                        | 61×10^9/L (count) | 1.5      | 487                    | N/A                | N/A               | N/A                               | N/A                                         | N/A                                       |
| Rokicka M. [28]   | IgG + 4                    | N/A              | N/A      | N/A                    | Not defined        | N/A               | 3 yr                               | Partially HLA matched                     | Minor ABO mismatch                         |
| Lewandowski K. [29]| N/A                        | 61.3 G/L (count) | 294      | Normal                 | N/A                | N/A               | N/A                               | N/A                                         | N/A                                       |
| Garg S. [30]      | N/A                        | N/A              | 408      | N/A                    | N/A                | N/A               | N/A                               | N/A                                         | N/A                                       |
| Cao L. [31]       | IgG + 1                    | 25               | 6,336    | N/A                    | >34                | N/A               | N/A                               | Unrelated HLA matched, major ABO mismatch  |                                            |

CML, chronic myeloid leukemia; AIHA, autoimmune hemolytic anemia; LDH, lactate dehydrogenase; HLA, human leukocyte antigen.
Discussion

The incidence of AIHA in patients with CML is extremely low, but when occurs, it almost always develops after the diagnosis of CML in the chronic phase. The rare occurrence and the variable onset of AIHA in those patients make it difficult to claim that CML per se is the main culprit. In terms of the possible underlying etiology, patients might be classified into 2 categories: the HSCT group, which constitutes more than half of the reported cases in this review, and the non-transplant group, which was treated with busulfan, interferon, or imatinib.

Hemolysis post-HCST is a rare but well-known complication and is categorized as either alloimmune or autoimmune [26]. The etiology of AIHA in the HSCT group is thought to be related to donor cell immune reconstitution [15, 26], concomitant viral infection, or CML relapse [17].

The cause of AIHA in the non-transplant group is thought to be linked to drugs used specifically for CML treatment, despite that the mechanism behind it is poorly understood. Interferon was more frequently reported to induce AIHA than both busulfan and imatinib combined, which gives an additional credit to tyrosine kinase inhibitors in terms of safety profile compared to older therapeutic agents. It was suggested that hemolysis, in case interferon was used, is mediated either by the formation of immune complexes or through the possible modification of RBC surface antigens and production of autoantibodies [32]. New onset severe anemia due to imatinib is very unusual [33]. It was hypothesized that the mechanism behind it is either due to the effect of imatinib on hematopoietic stem cells or through an interaction with iron absorption or metabolism, although iron replacement did not improve the outcome [34].

In terms of prognosis, many patients responded well to steroids as first-line treatment, but physicians should keep in mind that second- and third-line treatment might be required in transplanted patients. As a conclusion, clinicians should be aware that although AIHA is uncommon in CML patients, it should be in the differential diagnosis list for those who develop a sudden drop in Hb without a source of bleeding. It should be kept in mind that AIHA is more commonly induced by older CML therapeutic agents.

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Statement of Ethics

This review did not require approval by the institutional review board as there was no direct involvement of human subjects.

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Author Contributions

All authors contributed equally to this work.

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