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CASE REPORT

Aplastic anemia triggered by the Bruton tyrosine kinase inhibitor acalabrutinib in two patients with mantle cell lymphoma – A case report

Anna Nikkarinen | **Ingrid Glimelius**

Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Uppsala, Sweden

Correspondence
Ingrid Glimelius, Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Sweden.
Email: Ingrid.glimelius@igp.uu.se

Abstract

The use of Bruton's tyrosine kinase inhibitors (BTKi) is rapidly increasing for patients with mantle cell lymphoma (MCL). Side effects reported so far are usually manageable. However, here we present two cases of life-threatening aplastic anemia (AA) upon treatment with the BTKi acalabrutinib for MCL. The first patient died of neutropenic infection secondary to AA. The second patient was successfully treated with immunosuppressive treatment but the MCL relapsed shortly thereafter. AA is a potentially fatal complication that should be considered when patients present with pancytopenia during treatment with BTKi.

KEYWORDS
acalabrutinib, aplastic anemia, Bruton tyrosine kinase inhibitor, case report, mantle cell lymphoma, pancytopenia

1 | INTRODUCTION

Bruton's tyrosine kinase inhibitors (BTKi) have greatly improved the outcome for patients with mantle cell lymphoma (MCL)[1]. The use of BTKi in MCL is rapidly increasing and new indications are approved in several hematological malignancies. BTKis are also being investigated for solid tumors such as lung and breast cancer [2]. Even though side effects are usually manageable and self-terminating after dose reduction or termination of the drug, there is reason for caution.

Here we report two cases of life-threatening AA in patients with MCL upon treatment with the BTK-inhibitor acalabrutinib in Uppsala, Sweden.

1.1 | Patient 1

The first patient was a 79-year-old male. His medical history included Parkinson's disease which had been diagnosed three years prior to the diagnosis of MCL and he had a family history of systemic lupus erythematosus. He presented with enlarged lymph nodes on both sides of the diaphragm and was diagnosed with a classical MCL with moderate proliferation. Bone marrow (BM) aspirate showed 0.3% clonal B-cells, the cell content of the BM was 40%, CD4/CD8 ratio was 3.6 in BM and 6.2 in peripheral blood (PB). A next-generation sequencing (NGS) panel [3] was applied and revealed a germline mutation in *neurofibromatosis type 1* but no somatic mutations (Table S1). First-line treatment was started with capsule acalabrutinib 100 mg bid in combination with rituximab every 4 weeks. The tumor response was excellent with nearly complete radiological remission of the MCL. Flow cytometry of BM was performed with no malignant cells. PB CD4/CD8 ratio was 5.2, indicating low levels of CD8+ T-cells. The corresponding ratio in BM was 2.7. After 3 months of treatment, there was a slight thrombocytopenia and a rise in liver enzyme values (Figure 1). Acalabrutinib and rituximab were stopped but the thrombocytopenia aggravated to pancytopenia (hemoglobin 112 g/L, white blood cells [WBC] 0.7 $\times$ 10^9/L, platelet count 10 $\times$ 10^9/L, reticulocytes 44 $\times$ 10^9/L, and direct antiglobulin test

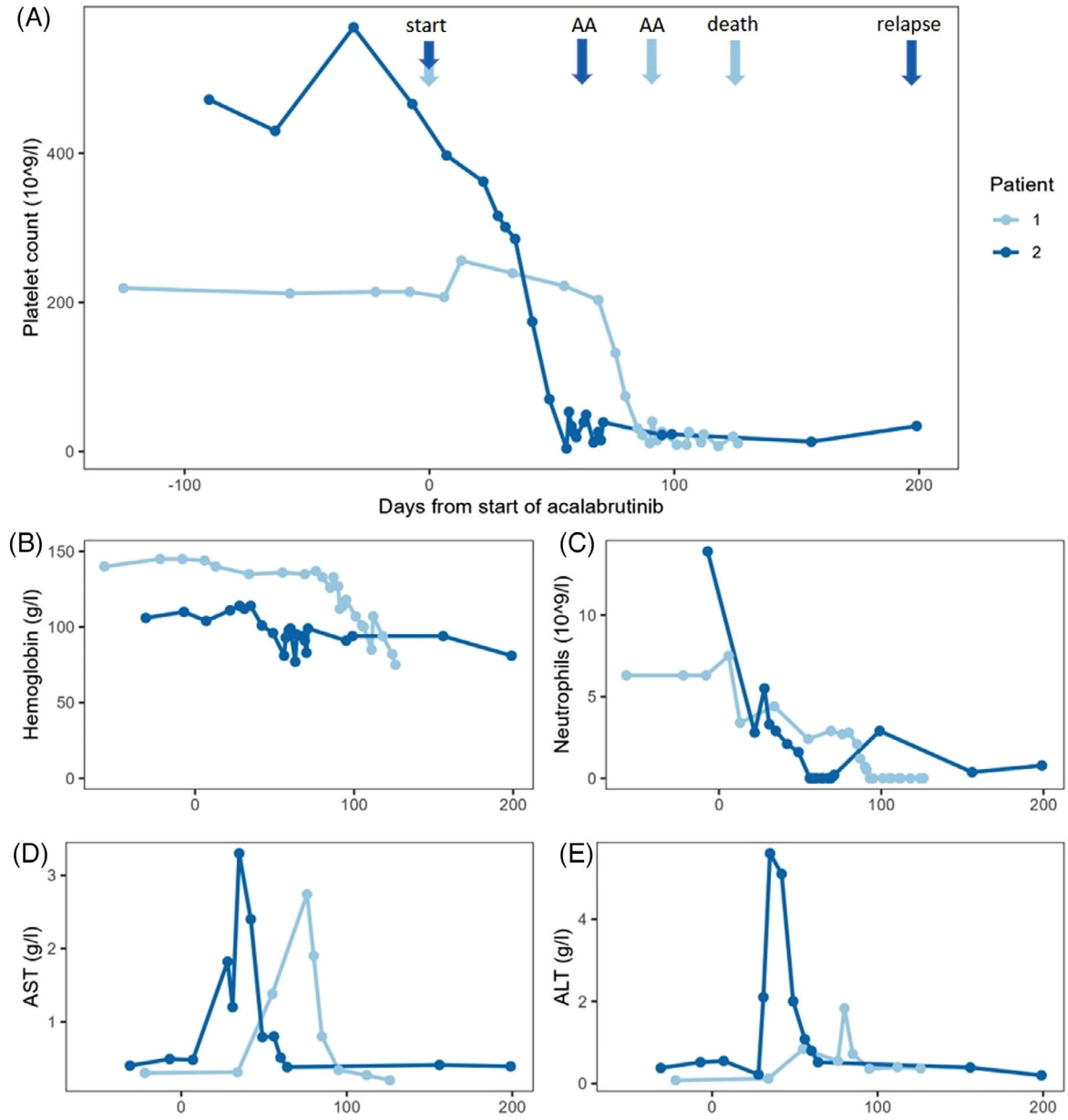

FIGURE 1 Peripheral blood values in relation to the start of acalabrutinib treatment. Decreases in both (A) platelet count, (B) hemoglobin values, and (C) neutrophil count were seen within a few months after the start of acalabrutinib. The peak of neutrophil count at day −7 for patient 2 was likely due to prednisone treatment and a small rise was seen at day 99 upon steroid treatment but as levels dropped again immunosuppressive treatment was started. Both patients had an increase in (D) AST and (E) ALT levels around 2 weeks before the decrease in peripheral blood values. The arrows indicate the start dates of acalabrutinib, dates of AA diagnosis, relapse of MCL, and death from AA. AST, aspartate aminotransferase; ALT, alanine transaminase; AA, aplastic anemia; MCL, mantle cell lymphoma.

[DAT] negative). The bone marrow was aplastic with cell counts < 10% and no malignant cells. The few available cells had a CD4/CD8 ratio of 2.5. Parvovirus B19 (DNA in BM < 160 IU/mL), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) were all negative. An NGS panel was applied again, without pathogenic mutations. Cytogenetic analysis was inconclusive, and analysis of glycosylphosphatidylinositol on neutrophils, erythrocytes, and monocytes showed levels below the detection limit (< 0.2%).

The diagnosis of AA was established. Treatment with prednisone 50 mg had no effect and after 4 weeks of pronounced pancytopenia, before specific immunosuppressive treatment was started, the patient died from septic shock.

1.2 | Patient 2

The second patient was a 77-year-old, previously healthy female. She was investigated due to gastric discomfort and was diagnosed with MCL with blastoid morphology and p53 overexpression. Her BM had 50% cell counts, 0.1% MCL cells by flow cytometry and the CD4/CD8

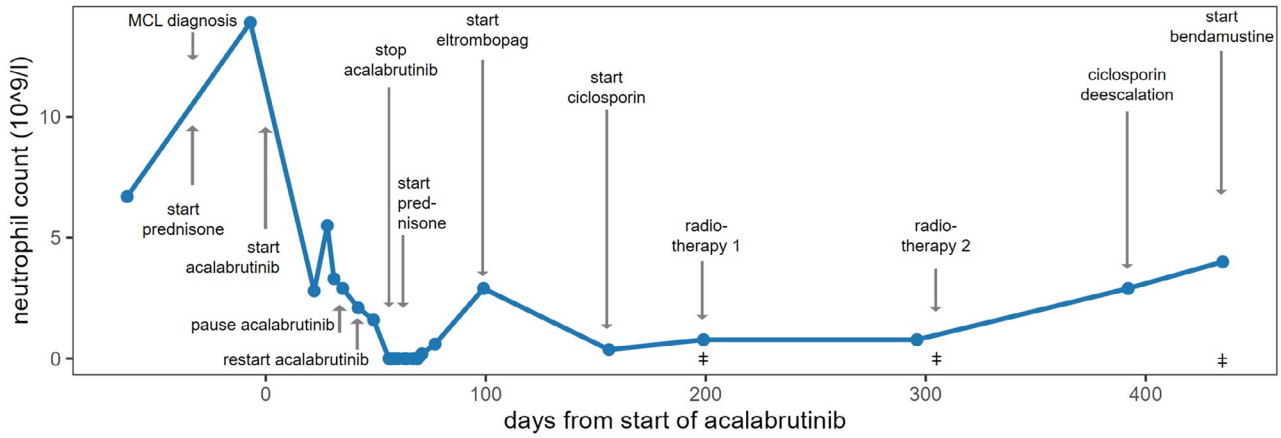

FIGURE 2 Timeline of neutrophil counts and the treatments given in patient 2. Prednisone 50 mg was started at diagnosis which explains the high value at the start of acalabrutinib. Acalabrutinib was paused due to high liver enzymes and restarted as AST and ALT levels were normalized, the neutrophil count was within normal range but then promptly dropped. Aplastic anemia was diagnosed 56 days after the start of acalabrutinib. High-dose prednisone had a moderate effect on the neutrophil count but platelet counts dropped as soon as prednisone was lowered and consequently, eltrombopag was started to control the thrombocytopenia. As neutrophil counts dropped again and transfusions had to be given more often, the patient was treated with cyclosporin. The first MCL relapse developed shortly thereafter (just before day 200), and was treated with radiotherapy (4 Gray × 2 fractions = 8 Gray). A second relapse 3 months later could also be treated with radiotherapy, but as MCL progressed at multiple locations (around day three hundred seventy) ciclosporin was deescalated. Ciclosporin de-escalation had no positive effect on the tumor burden and bendamustine was started with good antitumoral effect at first evaluation. ALT, alanine transaminase; AST, aspartate aminotransferase; MCL, mantle cell lymphoma; WBC, white blood cell.

ratio was 0.5 in BM and 0.3 in PB (Table S1). First-line treatment was started with acalabrutinib 100 mg bid in combination with rituximab. Her proton pump inhibitor was changed to an H2 receptor antagonist due to the risk of interaction. After 1 month, all gastric discomfort was gone but a rise in liver enzymes led to 2 weeks pause of acalabrutinib, whereby the liver enzymes were normalized and acalabrutinib was restarted (Figure 2). One week after restarting, the patient presented with hematomas and pancytopenia (hemoglobin 81 g/L, WBC 1.0×10^9/L, platelet count $< 5 \times 10^9$/L, and DAT negative). Hemophagocytic lymphohistiocytosis (HLH) was suspected at first. She received platelet and erythrocyte transfusions, and G-CSF injections daily for 1 week until a BM biopsy showed extremely cell-deficient bone marrow. The few cells were analyzed with flow cytometry as 66% T-cells, 37% natural killer cells, and 0.1% polyclonal B-cells. CMV, EBV, hepatitis, HIV, and parvo-B19 (DNA in plasma < 160 IU/mL) were all negative. An NGS panel showed no pathogenic variants. She was diagnosed with AA. Treatment with prednisone 1 mg/kg led to a slight improvement of both leukopenia and thrombocytopenia and the BM cell count was now 30%, with lively erythropoiesis. However, the platelet count dropped whenever prednisone was lowered below 40 mg daily. Eltrombopag was started and initially kept platelet levels acceptable, but after 2 months there was a higher demand for transfusions, consequently, treatment with ciclosporin was initiated. One month after the start of ciclosporin the first MCL relapse was evident. The patient received radiotherapy twice for local control. At the time of the second radiotherapy (Figure 2, day 308), flow cytometry of PB showed tumor cells at 0.01%, CD3+ T-cells at 17%, and a CD4/CD8 ratio of 1.0. Hemoglobin was 90 g/L, WBC 2.7×10^9/L, platelet count 27×10^9/L, and reticulocytes 45×10^9/L. Shortly thereafter, the MCL progressed at multiple locations. Bone marrow function was now almost normal and a de-escalation of ciclosporin was initiated with the intention to gain an immune response toward the tumor. Despite this, there was a massive progression of the tumor. As the patient now had acceptable peripheral blood values with steroids, systemic treatment with chemotherapy was started and led to a good partial remission of the MCL but with remaining signs of AA. She has had an aplastic bone-marrow for a total of 12 months at the time of summarizing this report.

2 | DISCUSSION

Here we present two cases of AA that developed within a few months after the start of the BTKi acalabrutinib. The first patient died of neutropenic infection secondary to AA. The second patient was successfully treated with immunosuppressive treatment but the MCL relapsed shortly thereafter. MCL progression in the bone marrow and viral infections were ruled out as causes for pancytopenia in both cases. In retrospect, the criteria for severe AA were clear in both patients already after the first BM examination. AA as a side effect of acalabrutinib was not expected and there was a hesitation to start specific immunosuppressive treatments due to the frailty of the patients, why corticosteroid treatment was used as first-line treatment.

Most cases of AA are considered idiopathic but there is a higher risk of AA among patients exposed to certain drugs, including chemotherapy [4]. In a phase II trial studying ibrutinib and rituximab for MCL, one patient developed AA after 5 months of treatment. This patient was younger and successfully treated with antithymocyte globulin

followed by allogeneic stem-cell transplantation. [5]. A phase I/II trial of acalabrutinib in MCL patients in China recently reported two cases of AA (one severe and one fatal), the treatment for AA is not specified in the report [6]. AA is also increasingly recognized as a side effect of tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia [7–9] and has been reported in at least two cases when TKI was given for lung cancer ([10, 11]). Rituximab is known to cause neutropenia but has, despite its extensive use, not been associated with AA in MCL [12]. Other autoimmune cytopenias, such as autoimmune hemolytic anemia, correlate with lymphoid malignancies. AA is however rare with only three reported cases in 1750 patients with chronic lymphocytic leukemia [13] and even lower rates in other non-Hodgkin lymphomas [14].

Potential mechanisms include inhibition of regulatory T-cells (T-regs) that are known to play a critical role in acquired AA [15]. Xia et al. suggested that T-reg inhibition by acalabrutinib could aggravate pre-existing autoimmunity [16].

As the use of BTKi in first-line settings is increasing, it is emerging that BTKi might be more toxic than we have previously seen in the relapsed/refractory setting, as seen in a study of ibrutinib and rituximab in older patients where 42% of the patients discontinued due to toxicities (no AA) [17].

In the case of AA due to BTKi in MCL patients, our suggestion is that AA should be treated aggressively and according to AA guidelines [18], despite the risk of triggering an MCL relapse.

This is one of the first reports of AA as a potential side effect of acalabrutinib in MCL, suggesting that it is rare. There is however a possibility that pancytopenia, especially later in the course of the disease, is falsely attributed to the progression of tumor infiltration in the bone marrow. AA is a potentially fatal complication that should be considered when patients present with pancytopenia during treatment with BTKi.

AUTHOR CONTRIBUTIONS

Ingrid Glimelius treated the patients. Anna Nikkarinen and Ingrid Glimelius reviewed the literature and wrote the manuscript. Anna Nikkarinen prepared the figures.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Not applicable.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

Both patients gave their informed consent to participate in this case report.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

ORCID

Anna Nikkarinen https://orcid.org/0009-0001-1451-0699
Ingrid Glimelius https://orcid.org/0000-0001-6158-3041

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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