

# An Unusual Case of a Hemolytic Crisis associated with the Initiation of an Aromatase Inhibitor in a Patient with Known History of Paroxysmal Nocturnal Hemoglobinuria

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**Abbreviations:** PNH: Paroxysmal nocturnal hemoglobinuria; AI: aromatase inhibitor; GPI-AP: glycosylphosphatidylinositol-anchored proteins; PIG-A: phosphatidylinositol glycan A; LDH: lactate dehydrogenase

## Abstract

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare hemolytic disorder characterized by partial or complete absence of the glycosylphosphatidylinositol-anchored proteins (GPI-AP) on the cell membrane of erythrocytes, platelets, and granulocytes rendering them vulnerable to destruction by the complement system. Various medications can provoke hemolytic crises in PNH or healthy subjects. Aromatase inhibitors (AI), which have revolutionized breast cancer management, are not known to trigger hemolytic crises. We report on a case of a 70-year-old female with PNH who was also diagnosed with breast cancer. Following lumpectomy and adjuvant radiation therapy, she was started on an AI to decrease risk of breast cancer recurrence. A few weeks later, she developed malaise, insomnia, and gross hematuria. Diagnostic workup including flow cytometry revealed a hemolytic crisis related to her PNH. An exhaustive investigation to uncover a potential mechanism that may explain the relation between AI initiation and onset of hemolytic crisis was unrevealing.

**Keywords:** Paroxysmal nocturnal hemoglobinuria, hemolytic crisis, aromatase inhibitor

## 1. Introduction

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare hemolytic disorder characterized by partial or complete absence of the glycosylphosphatidylinositol-anchored proteins (GPI-AP) on the cell membrane of erythrocytes, platelets, and granulocytes. The absence of this important protein renders these cells vulnerable to destruction by the complement system (Rosse, 1997). Clinical manifestations include intravascular hemolysis, cytopenia, thrombosis, and bone marrow failure (Parker, 2005). The absence of GPI anchors is due to somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene that code for the membrane protein (Takeda, 1993). There has been tremendous improvement in the understanding of the pathophysiology of the disease leading to new therapy aimed against complement-mediated cell lysis (Parker, 2005; Rother, 2007; Hillmen, 2006). Most crises are triggered by an infection or other stressful conditions that lead to complement activation. While various medications are known to also cause hemolytic crises, aromatase inhibitors (AI) are not cited in this category. Their introduction has changed management of breast cancer leading to increased survival (Mauri, 2006).

## 2. Case Report

We report on a case of a 70-year-old female diagnosed with PNH in her 50's after presenting with malaise, fatigue, and dark-colored urine at night time. She had significant drop in hemoglobin and elevated lactate dehydrogenase (LDH). Workup for immune-mediated hemolytic processes was negative; bone marrow biopsy and aspirate studies were unremarkable for any myelodysplastic process. The diagnosis of PNH was made based on positive hemolysis test per patient's report. During the 20-year period between diagnosis and current presentation, the patient experienced 3 additional hemolytic crises that were precipitated by either an upper

respiratory tract infection or dehydration. All cases were managed conservatively and resolved by treatment of the underlying causes; she had never required blood transfusion.

In 2010, she was diagnosed with invasive lobular right breast cancer; she underwent lumpectomy and radiation therapy. Given the estrogen receptor and progesterone receptor positive nature of her tumor, she was started on hormonal therapy with Anastrozole, an aromatase inhibitor in December 2010. Few weeks later, the patient developed malaise, insomnia, and gross hematuria at night. Despite symptomatic management, her condition continued to deteriorate to the point that she was experiencing significant back pain, restless legs, and the insomnia was affecting her quality of life. A laboratory evaluation revealed anemia with hemoglobin of 7.7 g/dL from a baseline of 11 g/dL, leukopenia with a white blood count of 1800 cells/ $\mu$ L, and an elevated LDH of 2075. Flow cytometry confirmed presence of CD55/CD59-deficient erythrocytes, monocytes, and granulocytes. Her PNH clone study revealed 56.5% type I (normal) RBC, 29% type II, and 14% type III. It is important to point out that the patient was not experiencing any fever, chills, cough, rhinorrhea, or any other signs or symptoms suggestive of a viral or bacterial infection. The patient had normal appetite, appropriate oral intake prior to onset of symptoms, and her initial evaluation was unremarkable for signs of dehydration. Given the correlation between the onset of symptoms and initiation of Anastrozole, the decision was made to discontinue the aromatase inhibitor. Her symptoms began to resolve after discontinuation of what was viewed as the offending agent.

Table 1. Laboratory data around the time of crisis showing sharp drop in hemoglobin level

	Aug 2008	Aug 2010	March 2011	March 2011	June 2011	July 2011	Sept 2011	Nov 2011	Feb 2012
Hg	11.4	11.1	7.7	8.5	6.4	9.6	10.3	11.1	10.4
Hct	35.3	33.0	24.1	25.5	20.2	28.4	30.0	32.4	34.7
WBC	4.0	6.2	1.8	3.3	3.1	3.1	3.1	3.0	3.6
Plt	208	185	113	111	132	145	153	150	138
LDH			2075	1443					248

Hg – hemoglobin in g/dL, Hct – hematocrit percentage, WBC – white blood cells in k/ $\mu$ L, Plt – platelets in k/ $\mu$ L, LDH – lactate dehydrogenase in IU/L

She was referred to our institution for further diagnostic evaluation and further therapy. Laboratory workup confirmed a Coombs negative hemolytic process. Bone marrow biopsy showed erythroid hyperplasia; other benign and malignant hematologic disorders were excluded. Despite resolution of her symptoms after discontinuation of Anastrozole, the hemolytic process persisted based on laboratory data with the hemoglobin value dropping to as low as 6.4 g/dL 3 months later. However, her blood count began to rise slowly afterward without further intervention. Treatment with Eculizumab was started in August 2011 to speed up recovery in order to prepare the patient for potential surgical intervention as new mammographic abnormalities were found on the opposite breast. She had a good response to therapy with further improvement in her blood count. She successfully underwent bilateral mastectomies in October 2011 without complication. Hormonal therapy with a different AI was re-introduced in December 2011; the patient remains asymptomatic.

### 3. Discussion

We searched the OVID/Medline database using the terms paroxysmal hemoglobinuria, hemolysis, and aromatase inhibitor. The search was limited to human subjects and English language. Searching these terms together revealed no result, so emphasis was placed on PNH pathophysiology, crisis precipitants including rare ones, relationship, if any, between PNH crises and the level of sex hormones. Anastrozole pharmacology, side effect profile, and expients were also reviewed.

As mentioned above, various conditions have been reported as hemolytic crisis precipitants in PNH patients; obviously, infections are the most common triggers due to activation of the complement system (Forman, 1984). Crises precipitated by many other stressful conditions have also been reported in literature; these include surgical interventions, menstruation, pregnancy, strenuous exercise, and dehydration (Dunn, 1991; Ito, 2011; Bais, 1994; Sola-Celigny, 1988). Other rare offenders, including pharmacological agents are also described in the literature (Morita, 1974; Berzuini, 2010).

There is however no prior report of a hemolytic crisis being triggered by aromatase inhibitors in healthy subjects or in patients with known history of hemolytic conditions. Extensive review of Anastrozole and other AI side effect profile from multiple sources was unremarkable for hemolysis or bone marrow suppression (Hillmen, 2006; Tamao, 2011; Perez, 2007). Finally, most of Anastrozole exipients are found in many other drugs and are known to be well tolerated.

Thus, we turn our attention to the potential effects of sex hormones on the immune system with a focus on complement activation and their potential effects on hematopoiesis. Again, no particular mechanism that can explain the reaction experienced by the patient was uncovered. Moreover, a recently published study demonstrates that estrogens exert their bactericidal activity in the uterus by activating the complement system (Rhen & Cidlowski, 2006). Although this is a local effect only; it seems counter-intuitive that lowering estrogen level by taking an AI would lead to PNH crisis unless there is an initial, brief up-regulation of aromatase action at the initiation of therapy.

After an exhaustive and unsuccessful search for probable mechanisms, we are simply left with few speculations. First, the increased level of testosterone because of aromatase inhibition may have led to increased hematopoiesis with production of more aberrant blood cells susceptible to destruction by the complement system. Second, an article published in the journal *Blood* by Calado and colleagues showed the effects of sex hormones on TERT genes and telomerase activity in human primary hematopoietic cells. The study demonstrates that Letrozole, an AI, blocks the telomerase stimulating action of androgens (Calado, 2009). Finally, the simplest explanation is that patient may have suffered an unrecognized viral illness at the time of the PNH crisis. This is supported by the fact that reintroduction of an AI did not cause further crisis.

#### 4. Conclusion

This case illustrates a common challenge that clinicians face when a patient develops an unexpected reaction after initiation of new therapy. While the first reaction and recommended action is to discontinue therapy, the decision is difficult to make when a life-saving treatment is involved, especially in the absence of a good alternative. In this case, there was a clear correlation between the initiation of AI regimen and the onset of a hemolytic crisis. However, in the absence of any clear mechanistic explanation for the adverse reaction, therapy was reinstated without further complication.

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