Acute leukemia in congenital methemoglobinemia - an enigma to explore

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ABSTRACT
Congenital methemoglobinemia is a rare disease, resulting in increased oxygen affinity and impaired oxygen delivery to the tissues. While there have been studies that have linked acquired methemoglobinemia in almost 79% of leukemia patients, to the best of our knowledge, this is the first case of leukemia development in a patient with congenital methemoglobinemia. Chronic deprivation of oxygen to metabolically active bone marrow can theoretically lead to hematopoietic disorders. It would be interesting to further investigate if presence of congenital methemoglobinemia is a risk factor for developing acute leukemia.

1. Background
Congenital methemoglobinemia is a rare disease resulting from cytochrome b5 reductase deficiency, cytochrome b5 deficiency or a mutation in globin molecule leading to hemoglobin M formation that leads to increased oxygen affinity and impaired oxygen delivery to the tissues [1].

In normal individuals methemoglobin level is below 1% (range 0–3%). However, levels may increase to above 10% in those with congenital disease. Pulse oximetry is not an accurate method to assess the level of oxygenation during this condition; consequently oxygen carrying capacity in such patients is determined using direct measurements of oxyhemoglobin by co-oximetry or arterial blood gas [2].

Hypoxia plays an important role in numerous pathological processes, including carcinogenesis, and metastasis [3]. Studies have shown acquired methemoglobinemia developing in almost 79% of leukemia patients. This is believed to be a result of increased oxidant stress generated by immature leukocytes (leukemic cells) leading to oxidation of heme from ferrous to the ferric state [2]. To the best of our knowledge, this is the first case of leukemia development in congenital methemoglobinemia.

2. Case description
A 74 year old Caucasian male with history of congenital methemoglobinemia (type 1 cytochrome b5 reductase deficiency) had presented to our hospital with symptoms of malaise, sweating, subjective fever, and productive cough. He failed to respond to antibiotics including 5 days course of azithromycin and additional courses of levofloxacin.

His pertinent physical exam later showed an acutely ill appearing male, pale with central and peripheral cyanosis, and vital signs showing afebrile, respiratory rate 19, hypoxemic with oxygen saturations of 79% while breathing on 7L litres per minute by Oxymask. His Abdominal exam was positive for distension with splenomegaly.

Pertinent Laboratory results showed elevated methemoglobin, leukocytosis with white blood cell count (WBC) 19.2K (H) which trended up to 86.7K associated with significant drop in oxygen saturation based on arterial blood gas (ABG) results from 90s to 80s on the third day of hospitalization. Peripheral blood smear and CBC revealed: macrocytic anemia, with nucleated erythrocytes, circulating blasts of 85% by morphology, and severe thrombocytopenia, and evidence of coagulopathy with increased INR and APTT. (Table 1)

Left posterior iliac crest bone marrows aspirate and core biopsy was sent to flow cytometry, cytogenetic (karyotype, AML FISH) and molecular (CEBPA, NPM1, IDH1/IDH2, FLT-3, RUNX1) studies.

- Pertinent findings: normal male karyotype: 46, XY, hypercellular marrow, 95% blasts, Acute myeloid leukemia with NPM1 and FLT3-ITD mutations, CD33 positive by flow cytometry
- Negative for (t 15;17) and (t5;17 or t11;17)

Pertinent imaging studies
- CT pulmonary study showed minimal bilateral sub-segmental pulmonary embolism, CT thorax
showed left lower lobe air space opacity, atelectasis versus consolidation (Figures 1 and 2)

- CT abdomen showed splenomegaly
- Doppler of lower extremity showed left deep venous thrombosis at mid distal popliteal vein.

### 3. Treatment

The patient had acute myeloid leukemia in the blast phase (48%) and was initially treated with allopurinol aimed to prevent tumor lysis syndrome. He was also started on hydroxyurea to help decrease leukostasis. Initially the patient was started on (7 + 3) cytarabine and daunorubicin, given that promyelocytic leukemia was not excluded, tretinoin was used. The patient was able to finish the chemotherapy induction. He was also noted to have a small PE and right lower extremity deep venous thrombosis that was initially treated with heparin drip. The goal of heparin therapy was also to get him through the initial phases of treatment with goal platelets greater than 30K. This unfortunately required daily platelet transfusions. After discussions with the patient and family, we decided to place an IVC filter temporarily. Heparin drip was continued with a new goal to continue heparin as long as the platelets were greater than 10k. The patient also had signs of clinical DIC and the goal fibrinogen levels were greater than 150.

However, his hospital course was complicated with continued worsening of respiratory failure, and increased oxygen requirement based on arterial blood gas analysis. This could not be explained by the small size of pulmonary embolism or the minimal pulmonary base opacity in the previous images.

During the hospital stay, he required multiple fresh frozen plasma, cryoprecipitate and platelet transfusions. The patient’s condition continued to deteriorate, and the final decision was to switch the patient to comfort care.

### 4. Discussion

Methemoglobin is associated with impaired oxygen delivery to the tissues due to increased oxygen affinity as hemoglobin oxidized from ferrous to ferric state [1]. Bone marrow oxygen levels in a healthy person range from 1 to 7%. Bone marrow hypoxia can alter cell

![Figure 1](image.png)

**Figure 1.** CT scan pulmonary artery study shows minimal bilateral sub-segmental pulmonary embolism.
death signaling pathways, increase the expression of anti-apoptotic proteins Mcl-1 and Bcl-2, modify proliferation activities and protein expression of cancer cells. Eventually it promotes survival of leukemic cells and resistance to chemotherapy and radiotherapy [4].

Several studies conducted on bone marrows of children with acute lymphoblastic leukemia (ALL) have shown increased expression of hypoxia-inducible factor (HIF-1α) that plays an important role in control glucose metabolism, angiogenesis and cell survival [5].

Our patient was diagnosed with type 1 cytochrome reductase deficiency since childhood, a condition that leads to increase levels of methemoglobin. Leukemia by itself can further increase methemoglobin level compared with baseline and eventually worsen tissue oxygenation. The mechanism underlying is increase oxidative stress as a result of elevated levels of free radicals which has been observed in almost all cancer cells, including immature leukemic cells [2,6].

As the patient developed acute leukemia, he started developing complications related to immature leukemic cells that manifested as thrombocytopenia, anemia and pulmonary embolism.

5. Conclusion

From the previous discussion, we know that there is an association between hypoxia and tumorigenesis through several mechanisms activities and protein expression of cancer cells. Eventually it promotes survival of leukemic cells and resistance to chemotherapy and radiotherapy. Some of the patients with congenital methemoglobinemia die early during adulthood. This limited life expectancy is especially seen in type 2 cytochrome B5 reductase deficiencies. The small population who live long enough to have a prolonged bone marrow hypoxia and potentially increased risk of developing acute leukemia. The occurrence of leukemia in congenital methemoglobinemia remains enigmatic.

Disclosure statement

No potential conflict of interest was reported by the authors.

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