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CASE REPORT

"Severe Anemia: A Case Report of an Uncommon Precipitant of Schizophrenia Relapse"

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Abstract: A 48-year-old patient with stable residual schizophrenia experienced a syndromic psychosis relapse following an episode of severe combined immunohemolytic and pure red cell aplastic anemia, with a hemoglobin level of 4.7 g/dl. The anemia was attributed to her anti-HIV medication zidovudine. Her HIV infection had been well-controlled; no other organic precipitant of the psychosis was found. Following transfusion of 2 units of leukocyte-poor packed red cells, schizophrenia symptoms promptly recovered to her baseline. This was maintained at 3- and 6-month follow-ups without any need for antipsychotic dose adjustment. Following zidovudine discontinuation and a short course of oral prednisolone, her anemia gradually recovered.

Keywords: neuropsychiatric, psychiatric, hematologic, zidovudine, HIV infection

Plain Language Summary

The authors describe a case of stable schizophrenia that had a relapse due to severe anemia. Blood transfusion resulted in quick and complete recovery to the patient's baseline.

Introduction

A recent estimate projected that anemia affects 26.8% of the population worldwide and is associated with 58.6 million years lived with disability, making it a public health concern. The signs and symptoms of anemia vary by severity, onset and chronicity, and etiology of the condition. End-organ symptoms from poor perfusion can be present in those with chronic or progressive anemia, causing symptoms such as fatigue, decrease in stamina, light-headedness, dyspnea, exercise intolerance, or syncope.[1] Affecting the brain, anemia can manifest with neuropsychiatric presentations including mood disorders, anxiety disorders, and psychoses.[2–6] Vitamin B12 deficiency, a cause of megaloblastic anemia, is known to cause psychosis regardless of the presence of anemia,[7–9] through mechanisms related to one-carbon metabolisms and syntheses of neurotransmitters.[10,11] Iron deficiency, another common entity, can affect dopamine receptor levels and disrupt functions of sensitive brain regions resulting in psychosis, again regardless of presence of anemia.[12,13]

Schizophrenia is a debilitating psychiatric disease with core symptoms of delusion and hallucination, affecting approximately 1% of the world's population.[14] At its onset, schizophrenia itself has been associated with low serum iron level, but not with anemia.[12,15] However, data on association between schizophrenia relapse and anemia are scarce. A PubMed search performed on 23 October 2022 with search string "(anemia OR anemic) AND (schizophrenia OR schizophrenic OR schizophreniform)" yielded 194 results, among which only one article was relevant: a case report of a known schizophrenia patient with multiple comorbidities presenting with hallucination from sickle cell crisis in 1991. The case passed away during the admission, hence there were no data on treatment effectiveness or follow-ups.[16] The current report complements the hematology literature on anemia and its role in triggering schizophrenia relapse.

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The Case

The patient is a 48-year-old female who was diagnosed with schizophrenia in 2014. Initially, multiple antipsychotics were consolidated due to her severe symptoms, and the regimen has been in place ever since due to the presence of residual symptoms (Table 1). Her residual symptoms have been stable and included auditory hallucinations with intact insight and reality testing. Since the first episode, she has displayed good treatment compliance and never experienced

Table 1 Timeline of Patient's HIV Infection and Schizophrenia

Time	Medical Conditions	Schizophrenia
Late 2012	Diagnosed with HIV infection. Received lamivudine, stavudine, and efavirenz. CD4+ 72 cells/ul. Prophylactic fluconazole and double strength co-trimoxazole given.	N/A
2013	Asymptomatic, no opportunistic infection. Decreased co-trimoxazole to single strength.	Infrequently had hallucinations and irritability associated with alcohol use. Has yet to receive formal diagnosis or treatment.
2014	Asymptomatic, no opportunistic infection. CD4+ 377 cells/ul. VL 85 copies/mL. Discontinued fluconazole and co-trimoxazole.	Displayed severe delusion and hallucination. Hospitalized. Schizophrenia diagnosed. Treated with 6 mg/day of risperidone, 100 mg/month of haloperidol decanoate, and 50 mg/month of fluphenazine. Became alcohol-abstinent ever since.
2015	Asymptomatic, no opportunistic infection. CD4+ between 575 cells/ul. VL 56 copies/mL.	Residual auditory hallucinations with intact insight. No delusion or disorganized behavior. Functioned stably in housekeeping. Antipsychotic drug regimen unchanged. Good compliance
2016–2019	Asymptomatic, no opportunistic infection. CD4+ 880–1082 cells/ul. VL <40 copies/mL.	Stable
2020	Anti-HIV drugs were changed to lamivudine, zidovudine, and efavirenz due to supply issues. Asymptomatic, no opportunistic infection. CD4+ 1935 cells/ul. VL <20 copies/mL.	Stable
2021 – January 2022	Asymptomatic, no opportunistic infection. CD4+ 1270–1317 cells/ul. VL <20 copies/mL.	Stable
April 2022	Unremarkable. Reportedly compliant to treatment.	Increased irritability. Loss of insight into own condition. Responded to hallucination. Slow thinking and speech. Decreased housekeeping ability. Reported headache, fatigue, and cold intolerance. Reportedly compliant to treatment.
May 2022	Unremarkable. Reportedly compliant to treatment.	Increased headache and fatigue. Visited ER. Dismissed as schizophrenia relapse. No investigation carried out.
June 2022	Combined immunohemolytic and pure-red cell aplastic anemia were found; Hb 4.2 g/dl. Hospitalized. Received 2 units of LPRC; Hb raised to 7.8 g/dl. Zidovudine was implicated and discontinued. Anti-HIV regimen changed to tenofovir, emtricitabine, and efavirenz. Started on 60 mg/day of prednisolone for immunohemolysis.	Visited psychiatric OPD which led to investigations. Psychotic symptoms promptly improved after transfusion. No psychiatric medication changes. Discharged after 2 days.
July 2022	HIV: asymptomatic. No anemic symptoms. Hb was 7.3 g/dl with no signs of ongoing hemolysis. Prednisolone continued at same dose.	Stable (same as 2015–2021 baseline)

(*Continued*)

Table 1 (Continued).

Time	Medical Conditions	Schizophrenia
August 2022	HIV: asymptomatic. No anemic symptoms. Hb rose to 10.6 g/dl with no signs of ongoing hemolysis. Prednisolone discontinued.	Stable
September 2022	HIV: asymptomatic. No anemic symptoms.	Stable
December 2022	HIV: asymptomatic. No anemic symptoms. Hb rose to 12.0 g/dl with no signs of ongoing hemolysis. Normal reticulocyte counts.	Stable

Abbreviations: CD4+, CD4+ positive cell counts; VL, HIV viral loads; LPRC, leukocyte-poor packed red cell; Hb, hemoglobin level.

relapse. The clinical global impression-severity was 2 (borderline ill) and clinical global impression-improvement was 1 (marked improvement from initial encounter). The patient functioned stably in her housekeeping duties.

Her medical history was significant for HIV infection, which was diagnosed in 2012. Initial CD4+ count at the time of diagnosis was 72 cells/ul, which rose to 377 cells/ul in the first year of treatment with lamivudine, stavudine, and efavirenz. She never had any opportunistic infection. Past self-reported pill counts indicated excellent compliance. Antiretroviral regimen was changed once owing to changes in locally available formulary (Table 1) to lamivudine, zidovudine, and efavirenz in 2020. In the past 3 yearly laboratory investigations, her CD4+ cell counts were between 1163–1935 cells/ul and viral loads were all < 20 copies/mL. She had no other underlying diseases.

The current relapse began 2 months prior. Her daughter noted that the patient started to respond to (the ever present) hallucinations while becoming more irritable, yet displayed slower responses to stimuli; these symptoms did not show any signs of fluctuation, nor were disorientations noted. The patient reported that her hallucinations occurred more frequently, and that she lost the ability to differentiate between hallucinations and reality. She also complained of fatigue, headache, and cold intolerance. Noncompliance was ruled out as the daughter noted that the patient regularly took her medicines and went for monthly injections while remaining pill counts were consistent with follow-up visit date. The patient was brought to the emergency department twice for her somatic complaints. In both instances, two separate physicians focused more on the relapse of psychotic symptoms and only prescribed intramuscular haloperidol without performing laboratory investigation before discharging the patient. The patient later came for a regular psychiatric follow-up visit and reported the relapse and somatic symptoms. The psychiatrist ascertained that there was no compliance issue, nor was there comorbid use of tobacco, alcohol, or illicit substances that could have triggered a psychotic episode or affected pharmacokinetics of the prescribed medication. Examination was positive for systolic ejection murmur. There was no thyroid enlargement, peripheral edema, or abnormalities in lung auscultation. Neurological examination was normal. Investigation revealed a hemoglobin level of 4.7 g/dl with multiple microspherocytes seen in peripheral blood smear; there was no history of hereditary spherocytosis or notes of spherocytes in complete blood counts in the past 10 years. Direct Coomb's test was positive (3+). Reticulocyte count, however, was not elevated (reticulocyte 0.24%, absolute count 3000 cells/ul). Iron studies were normal. Vitamin B12 level was within intermediate range and was deemed unexplanatory of the low reticulocyte count. (The cause of borderline low vitamin B12 was attributed to her self-medication with omeprazole for dyspepsia). Combined autoimmune hemolytic anemia and pure red cell aplasia attributed to zidovudine was provisionally diagnosed. Infectious specialist ruled out possibilities of anemia and psychotic symptoms from HIV, as her infection had been under good control. As her homocysteine level, the marker of abnormality in one-carbon metabolism pathway and the implicated mechanism of psychosis from vitamin B12 deficiency, was within normal range, psychosis from the vitamin status was ruled out. No abnormalities were seen in serum electrolyte panels, thyroid functions, and liver functions, nor was there rhabdomyolysis as evaluated by serum creatine phosphokinase, lactate dehydrogenase and urine myoglobin, ruling out their contribution to psychosis and somatic symptoms.

Transfusion with 2 units of leukocyte-poor packed red blood cells was initiated. After her hemoglobin level rose to 7.8 g/dl over the course of the night the transfusion was carried out, her psychotic symptoms promptly abated: frequency

of hallucination became rare, insight and reality testing returned, and mood and affect became euthymic. The recovery was maintained throughout the admission. No adjustment in psychiatric medication was necessary. As zidovudine was implicated as etiology of anemia, the anti-HIV regimen was changed to tenofovir, emtricitabine, and efavirenz. 60 mg/d of prednisolone was given for immunohemolysis. At 2-week follow-up her hemoglobin level was similar to post-transfusion (7.3 g/dl) without any ongoing signs of hemolysis in blood smear, and schizophrenia symptoms were stable. At 3-months, and 6-months follow-ups, her schizophrenia remained in quiescence and her anemia gradually improved (Table 1). Self-reported compliance and leftover pill counts indicated good compliance.

Ethical Considerations

This case report was approved by Human Research Ethics Committee of Srinakharinwirot University (number: SWUEC-M-075/2565E). Written informed consent for publication of case details and any accompanying images was obtained from the patient during the period of stable psychiatric symptoms as per the ethics committee's approval. The authors' institution did not require approval to publish case detail.

Discussion

Zidovudine and Anemia

Anemia in the present case was attributed to zidovudine. The agent is known to cause anemia from multiple mechanisms, including immunohemolysis and bone marrow suppression. Latency from drug initiation can be years,[17–21] which is consistent with presentation in our case. HIV infection itself has also been associated with development of immunohemolysis but only in severely immunocompromised hosts,[22,23] which is unlikely as the patient's HIV infection had been under good control.

Immunohemolysis was evident from direct Coomb's test and typical peripheral blood smear. Pure red cell aplasia, another anemic condition known to be triggered by zidovudine, was inferred from the lack of reactive reticulocytosis to the 2-month course of anemia despite the absence of nutritional deficiency. The absence of bone marrow study results in this case, however, precluded a firm diagnosis of the latter condition.

Different Causes of Anemia and Psychosis

Reports on psychosis from anemia are still sparse. Most were related to megaloblastic anemia associated with vitamin B12 and folate deficiency ("megaloblastic madness").[24] Historic cases reported that psychoses in pernicious anemia were treatable with electroconvulsion.[25,26] The response to the same treatment as schizophrenia spectrum psychoses may imply shared pathological processes. More recently, a report described a case with megaloblastic anemia presenting as subacute disorganized behaviors and memory impairment. The case improved after three days of vitamin B12 administration.[27] Normalization of hematopoiesis could not have occurred in such short period. This is also consistent with other reports in which psychoses occurred in isolated vitamin B12 deficiency without megaloblastic anemia,[28–30] pointing to the deficiency's independent effect such as homocysteinemia due to problems in one-carbon metabolisms or abnormalities in synthesis of neurotransmitters.[10,11,31] Similarly, the widely studied iron deficiency anemia is also implicated as the predisposing factor of schizophrenia,[32–34] but the mechanism driving development of psychosis appears to be from iron status deviating brain developmental trajectories.[13,35–37] Therefore, psychoses from these two entities likely followed mechanisms different from that of the present case.

There is a report of a case with exacerbated chronic familial hemolytic anemia (hemoglobin 3.7 g/dl) following *Clostridium perfringens* sepsis which caused psychosis. In contrast to our case, this patient developed paranoid psychosis, aggression, and disorientation after transfusion, and only improved with subsequent antibiotics treatment.[38] The clinical picture is likely that of delirium (as opposed to our case), which can be attributed to either anemia, sequelae of hemolysis, transfusion reaction, and/or sepsis.

A similar clinical situation was reported in a stable schizophrenia patient who developed combined megaloblastic and autoimmune hemolytic anemia. Despite having similarly low hemoglobin level (initially 6.5 g/dl, later dropped to 5.4 g/dl), this patient did not experience relapse of psychotic symptoms as reported in the present case despite having

hemoglobin level only slightly higher than our case.[39] The report stated that the patient's psychosis was in remission, a different baseline from our case whose residual symptoms had been present. The residual symptoms point to a more severe pathology that required greater compensatory functions and, possibly, a greater vulnerability to any loss.

Anemia, Cognitive Functions, and the Link with Psychological Insight

The mechanism by which anemia induced psychosis in the present case was possibly different from those in micronutrient deficiency or sepsis. The possibility that autoimmunity status mediated the exacerbation is also unlikely, as the psychosis resolved prior to initiation of prednisolone. We hypothesize the mechanism of impairment and recovery of cognitive function explaining the relapse and prompt recovery with transfusion. As previously noted, the patient's insight and reality testing only became impaired during this episode. In modern sense, the psychoanalytic-inclined term of reality testing and insight has now been viewed as an expression of cognitive functions.[40–42] Recent views on schizophrenia have implicated the decline in cognitive functions as one of the triggers of conversion from high-risk states (including attenuated psychosis syndrome and brief limited intermittent psychotic symptoms) to schizophrenia.[43] If so, a decline in sensitive cognitive functions in a patient with established disease should also be able to trigger a schizophrenia relapse. In this case, the role of anemia was apparent. Anemia disrupts the oxygenation of the central nervous system, impairing cognitive functions. Two experiments examined reaction time and memory in iatrogenically-produced acute normovolemic anemia. These cognitive functions started to decline subtly at hemoglobin level of 6 g/dl (approximately 8 g/dl below mean pre-dilution concentration). Autotransfusion reversed the impairment, while administration of supplemental oxygen alone could also create partial improvement.[44,45] This suggests that poor oxygenation contributed to the deficits. A further experiment found that the impaired cognitive functions were attributable to impaired central processing.[46] Although these studies have yet to explore the anemia's and transfusion's effects on other cognitive domains, it can be presumed that deficits and recoveries occur simultaneously. Unfortunately, these studies explored changes in cognition in short-term anemia. The present case's anemia had likely developed over the past two months and whether the experiment's findings are generalizable is not known. Chronic anemia can be followed by compensation and decompensation processes which can distort its effects on cognitive functions related to psychological insight. Nevertheless, data from commonly encountered chronic anemia such as iron deficiency, end-stage renal disease, sickle cell anemia, and thalassemia seem to indicate the presence of cognitive disturbances in these entities as well, although their disease-specific pathophysiology may also be operating on top of anemia itself.[47–51] Chronic anemia in the elderly and oncologic patients has also been associated with reversible cognitive deficits.[52,53]

The Present Case and Implications

From the psychiatric perspective, a disease relapse is a function of risk factors. For schizophrenia, common risk factors are medication discontinuation and substance use, which were not present in this case. Another strong factor is the disease's chronicity, which is assumed to be accompanied by ongoing pathological processes such as low-grade systemic inflammation and brain function deterioration.[54–59] Moreover, the chronic use of antipsychotics and the patient's sedentary lifestyle could have led to metabolic derangements, potentially worsening the inflammatory condition.[60] Her HIV infection, although well controlled, can also exert subtle inflammatory disturbances that chronically deteriorate brain function and adds to the predisposition.[61] These factors are then precipitated into a syndromic relapse by the emergence of severe anemia.

From her course of physical symptoms and relatively preserved level of consciousness, it was suspected that her anemia may have been gradually progressing over the past two months, concurrent with the re-emergence of psychotic symptoms. Due to the absence of symptom fluctuation and disorientation, the psychosis was unlikely a part of delirium. Therefore, the re-emergence of symptoms was diagnosed as schizophrenia relapse. Her reality testing, insight, and auditory hallucination recovered to baseline after transfusion raising hemoglobin level from 4.2 to 7.8 g/dl. The rapid improvement of insight could be a product of recovery of sensitive cognitive functions, similar to situations observed in iatrogenic normovolemic anemia experiments. Hallucination has been postulated as a disorder of brain regions generating inner speech, while the insight or the ability to tell hallucination apart from reality is an amalgam of self-certainty, self-reflection, executive functions, and memories.[62] Apparently, the scope far exceeds those studied in iatrogenic anemia;

what we can assume from the phenomenon in this case is that said cognitive functions (and responsible brain regions) are sensitive to hypoxemia. Nevertheless, ascertaining whether schizophrenia relapses can occur from transient cognitive decline from anemia requires further studies. Moreover, whether the brain's reactive or autoregulatory changes toward anemia (vascular, metabolic, hormonal, etc) contribute to risk or protection of relapses also requires further studies.

There is also a paucity of reports of anemia triggering relapse in cases of established psychiatric illnesses other than schizophrenia. Generalizing about this suggested mechanism of impaired cognitive function, clinicians encountering anemia may also look for emergence or relapse of other psychiatric diseases in which cognitive dysfunctions play substantial roles, such as depression, anxiety, and neurocognitive disorders.[63–68] These conditions involve different cognitive domains as opposed to schizophrenia which may become impaired at a different severity of anemia.

For clinicians encountering relapses of schizophrenia or mood disorders, consideration should be given that anemia could be among the differential diagnoses. When occurring in concert with anemia, correction of anemia alone may resolve these psychiatric symptoms. Psychotropic medication adjustment may be unnecessary or only used judiciously for temporary stabilization of severe agitation. For psychiatrists, monitoring for signs of anemia, surveillance of blood counts when indicated, and prompt referral for hematological treatment will serve to complement biological aspects of psychiatric care.

Limitations

There were limitations in the definite diagnosis of anemia in the present case. The onset was presumed from somatic symptom history. The comorbid diagnosis of pure red cell aplasia was presumptive and lacked bone marrow study data. Although much rarer than zidovudine-induced one, HIV-related immunohemolysis in well controlled cases remained a possibility. The possible underlying HIV infection-associated brain pathology and subsequent predisposition toward triggers of decompensation might differentiate the case from typical schizophrenia patients.

Conclusion

A case of a stable schizophrenia patient who experienced relapse following severe anemia from zidovudine-related immunohemolysis and red cell aplasia was described. Schizophrenia symptoms promptly returned to baseline following transfusion and did not necessitate changes in psychiatric medication; symptoms remained stable over 6 months of follow-ups. Clinicians encountering schizophrenia relapses may also evaluate their patients for anemia; such psychoses may be promptly reversible as reported in this case.

Disclosure

The authors report no conflicts of interest in this work.

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