A Rare Case of Hypoparathyroidism and Myxedema Coma in a Patient With Diamond-Blackfan Anemia

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Abstract

Diamond-Blackfan anemia (DBA) is a rare genetic condition that presents due to bone marrow failure caused by a dysfunction in ribosomal biogenesis and function. The patients would often require chronic transfusions as treatment, which puts them at high risk for the development of secondary hemochromatosis. This secondary hemochromatosis results in endocrinopathies due to iron deposition into the endocrine glands. We present an interesting case report of a female patient with multiple endocrinopathies due to secondary hemochromatosis resulting from chronic transfusion therapy. Her endocrinopathies included hypothyroidism complicated by myxedema coma and, interestingly, hypoparathyroidism, which has seldom been reported in DBA patients. Early diagnosis and precise treatment of life-threatening conditions like myxedema coma in DBA patients can avoid morbidity and mortality.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine, Oncology
Keywords: internal medicine and endocrinology, blood transfusion safety, myxedema coma, diamond-blackfan anemia, hypothyroidism

Introduction

Diamond-Blackfan anemia (DBA) is a rare genetic condition that results from bone marrow failure, due to a dysfunction in ribosomal biogenesis and function. The patients of this condition need to undergo chronic transfusions as treatment, which puts them at high risk for the development of secondary hemochromatosis. This secondary hemochromatosis leads to endocrinopathies because of iron deposition into the endocrine glands. This deposition of iron causes malfunction of endocrine glands causing the patient to suffer from multiple endocrinopathies.

Case Presentation

A 22-year-old female with a pertinent medical history of DBA and chronic hepatic thrombosis (on anticoagulation with Eliquis) was admitted to the hospital for left upper back cellulitis. Unfortunately due to her anemia (baseline hemoglobin: 9 g/dl), she had required transfusions with packed red blood cells every three to four weeks and was also on daily chronic chelation therapy with deferasirox; her last transfusion had been four days before the admission. Her history was further complicated by multiple endocrinopathies including hypothyroidism, hypergonadism, growth hormone deficiency, and insulin-dependent diabetes mellitus. On admission, the patient’s vital signs were normal. Her initial blood work included a metabolic panel (Table 1) revealing hyperglycemia, hypocalcemia, high phosphorus, and transaminitis. Findings on a CT scan of the chest correlated with cellulitis overlying the left trapezius muscle for which empiric treatment with broad-spectrum IV antibiotics was initiated. She was subsequently started on subcutaneous weight-based insulin for hyperglycemia, calcium supplementation through calcium drip at 50 cc/hour of calcium gluconate for 24 hours; an electrocardiogram was done, which revealed normal sinus rhythm, and an ultrasound of the liver was performed, but it revealed no obvious abnormalities, deeming her transaminitis likely a result of chronic hepatic thrombosis combined with hepatic iron deposits from chronic transfusions.
On day two of her hospitalization, a rapid response was called on the patient as she fell backward from a sitting position and became unresponsive. She was placed on a monitor, which revealed sinus bradycardia with a heart rate of 36 bpm and hypotension with a blood pressure of 68/40 mmHg. Her pulse oximeter was 100% on a non-rebreather. TPA was held due to her being on anticoagulation. Within a few minutes, she became responsive but revealed poor motor response on physical exam with diminished reflexes. She was taken for a CT scan of the head along with a CT perfusion study of the head, but both revealed no acute findings. Blood work was performed, which included tests for thyroid-stimulating hormone (TSH), free thyroxine (FT4), T3, complete blood count (CBC), blood cultures, an 8-am cortisol level, and a metabolic profile. On the morning of hospital day three, the patient became unresponsive again. Vital signs were again significant for bradycardia and hypotension. She remained unresponsive for a few minutes and then quickly returned to baseline. Her physical exam persistently revealed diminished reflexes bilaterally. The patient was managed for possible seizure activity and was loaded with levetiracetam, and an electroencephalogram (EEG) was performed, which revealed normal results. Later in the day, her laboratory results for thyroid function came back and were significant for an elevated TSH and a suppressed FT4 (Table 2).

The patient’s history was taken again by the covering physician, and she revealed a history of hypothyroidism along with non-compliance with her home dose of 100 mcg of levothyroxine. On further review of her medical records, it was found that she was negative for anti-thyroid peroxidase antibody, and an ultrasound of the thyroid gland from last year was non-revealing of any thyroid nodules. She was seen by endocrinology, who attributed her condition to myxedema coma. The patient did not have a baseline 8-am cortisol level result, and hence she was given a stress dose of 100 mg of IV hydrocortisone and started on a standing dose of 100 mg hydrocortisone every eight hours. She was then given a bolus dose of 400 mcg IV levothyroxine, put back on her home dose of oral levothyroxine, and started on triiodothyronine 5 mcg twice daily. She improved clinically in the next three days and her morning cortisol drawn before treatment was

### TABLE 1: Metabolic panel

| Variables     | Reference range          | Patient value |
|---------------|--------------------------|---------------|
| Calcium       | 8.7–10.5 mg/dL           | 6.8           |
| Phosphorus    | 2.1–4.9 mg/dL            | 9.7           |
| Albumin       | 3.4–5.4 g/dl             | 4.2           |
| AST           | 10–40 u/l                | 114           |
| ALT           | 4–36 u/l                 | 118           |
| Bicarbonate   | 22–28 meq/l              | 21            |
| Hemoglobin A1c| 4–5.6%                   | 9.8           |
| Glucose       | Less than 100 mg/dl      | 428           |
| Anion gap     | 3–10 meq/l               | 7             |
| Creatinine    | 0.6–1.2 mg/dl            | 1.2           |
| GFR           | Greater than 60          | >60           |

**AST:** aspartate aminotransferase; **ALT:** alanine aminotransferase; **GFR:** glomerular filtration rate

### TABLE 2: Thyroid function test

| Variables | Reference range         | Patient value |
|-----------|-------------------------|---------------|
| TSH       | 0.400–4.000 mIU/mL      | 288           |
| Free T4   | 0.71–1.9 ng/dL          | <0.1          |
| T3        | 80–200 ng/dl            | <20           |

**TSH:** thyroid-stimulating hormone
initiated came out to be normal (16 mcg/dl). Her triiodothyronine, antiepileptic medication, and hydrocortisone were gradually tapered off. Her blood cultures came out positive for methicillin-sensitive *Staphylococcus aureus* and she completed a course of antibiotics for the underlying cellulitis. Given her studies were significant for hypocalcemia and elevated phosphorus, parathyroid hormone (PTH) was checked during her hospitalization. The PTH results showed a suppressed intact PTH (Table 3) and confirmed our suspicion of hypoparathyroidism in her. After initially being placed on a drip of calcium gluconate, she was started on daily oral calcium carbonate, which was asked to continue on discharge. She was also started on calcitriol 0.5 mcg daily. She was advised on the importance of compliance with her medications and to have a close follow-up with her endocrinologist on discharge.

| Variables               | Reference range | Patient value |
|-------------------------|-----------------|---------------|
| Calcium                 | 8.7–10.5 mg/dL  | 6.8           |
| Phosphorus              | 2.1–4.9 mg/dL   | 9.7           |
| Albumin                 | 3.4–5.4 g/dl    | 4.2           |
| Vitamin D, 25 OH        | 30–80 ng/mL     | 8             |
| Vitamin D, 1,25 OH      | 19.9–79.3 ng/mL | 5             |
| Parathyroid hormone     | 15–65 pg/ml     | 2             |

**TABLE 3: Laboratory results**

**Discussion**

DBA is an extremely rare syndrome, which affects five to seven per million live births per year [1]. It was recognized as a distinct clinical entity in 1938 and classified as one of the rare inherited bone marrow failure syndromes [2]. The syndrome is a result of a cellular defect in which erythroid progenitors and precursors are highly sensitive to death by apoptosis leading to an erythropoietic failure. It is characterized by bone marrow failure, congenital anomalies, and predisposition to cancer. A variety of congenital anomalies including craniofacial, ophthalmologic, urogenital, cardiac, and neuromuscular have been reported. Craniofacial is the most common, involving 50% of all reported congenital anomalies. DBA is believed to be a disorder of ribosome biogenesis and function with 50% of patients having a single gene mutation in the gene encoding a ribosomal protein. The most common mutation reported involves RPS19 [3]. It is mainly inherited through an autosomal-dominant pattern, but there have been cases with sporadic or different patterns of familial inheritance.

The initial treatment of DBA begins at the age of one with corticosteroids. Prednisone is started at a dose of 2 mg/kg/day and gradually reduced to <0.5 mg/kg/day. Roughly 80% of patients respond to steroids given as the initial course, but only 40% have a sustained response without dose-limiting toxicity. The chronic use of corticosteroids therapy predisposes these patients to iatrogenic Cushing’s syndrome and adrenal insufficiency. Chronic transfusion therapy is usually initiated in DBA patients once it has been established that they are no longer responsive to corticosteroids. Importantly though, if chronic transfusion therapy is initiated, the corticosteroid regimen is tapered off and discontinued. Unfortunately, around 40% of these patients become transfusion-dependent, requiring packed red blood cells every three to four weeks [1]. Furthermore, on reviewing the literature, the role of hematopoietic stem cell transplant remains controversial in these patients. The use of chronic blood transfusions places DBA patients at risk for secondary hemochromatosis, which can lead to a variety of different complications. About 23% of all deaths reported to the DBA American Registry are related to complications from iron overload [4]. It has been found in the literature that around 20% of patients enter remission and require neither corticosteroids nor transfusions for longer than six months.

Endocrinopathies can develop as a result of direct iron deposition into endocrine glands and have been reported in a few studies [5]. A French cohort study revealed that 14% of DBA patients developed iron-related endocrine or other organ complications, and an Italian cohort study revealed that 23% of DBA patients developed the same [1,5,6]. To help minimize these complications, chelation therapy is often initiated. However, despite chelation therapy, complications from iron overload and endocrinopathies are still reported in these patients [7,8]. Reviewing a report from the DBA Registry, it was seen that 53% of DBA patients were found to have one or more endocrine disorders present in them. Of note, 45% of chronically transfused patients had endocrinopathies with the most common being adrenal insufficiency. This adrenal insufficiency was noted more in the patients receiving chronic glucocorticoid treatment. Hypogonadism and hypothyroidism were the second and third most common endocrinopathies seen in these patients.

Our patient had multiple endocrinopathies including hypothyroidism, hypogonadism, growth hormone...
Hypoparathyroidism is an extremely rare complication of transfusion-dependent patients. It occurs as a result of iron deposition into the parathyroid gland. The dysfunction of the parathyroid leads to deficient secretion of PTH, resulting in absent signaling in classic target tissues [14]. In the study done by the DBA Registry, there were no patients diagnosed with hypoparathyroidism; however, there was heavy suspicion in two patients [1]. Hypoparathyroidism, though, has been reported in patients with transfusion-dependent thalassemia as well as in a French cohort study on DBA patients [6]. Diagnosis can be made with low serum ionized or albumin correct calcium concentration with a low or undetectable PTH. Our patient had a low PTH with low corrected calcium, which was consistent with a diagnosis of hypoparathyroidism.

Conclusions

DBA is a rare genetic condition occurring due to marrow failure. The patients are often required to undergo chronic transfusions for treatment, which puts them at high risk for the development of secondary hemochromatosis. Our patient presented with hypoparathyroidism, which has not been reported in a DBA patient before, based on our elaborate review of the literature. Early diagnosis and precise treatment of life-threatening conditions like myxedema coma and hypoparathyroidism in DBA patients can help us save their lives.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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