Steroid-associated bradycardia in a newly diagnosed B precursor acute lymphoblastic leukemia patient with Holt–Oram syndrome

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ABSTRACT

Holt–Oram syndrome (HOS) (OMIM#142900) is a rare condition with upper extremity malformations as well as structural and conduction cardiac anomalies. There are sparse reports in the literature documenting malignancy in association with HOS. We report a pediatric patient clinically diagnosed with HOS (missing thumbs bilaterally, atrial septal defect, ventricular septal defect, and first-degree heart block), who also developed B precursor acute lymphoblastic leukemia. During induction of chemotherapy with steroids, she developed profound bradycardia without clinical symptoms. The bradycardia resolved without intervention, but this case highlights the challenges of managing chemotherapy side effects in a patient with congenital heart disease. A literature review pertinent to the associated findings in the case is also presented.

Keywords: Acute lymphoblastic leukemia, bradycardia, Holt–Oram, steroid-associated bradycardia

INTRODUCTION

Holt–Oram syndrome (HOS) is a rare autosomal dominant condition that was first identified in a family with generational anomalies of the upper extremity, arrhythmias, and suspicion of atrial septum defects.[1] Few cases of malignancy have been documented previously in association with this syndrome, and to the best of our knowledge, we document the first case of B precursor acute lymphoblastic leukemia (B-ALL) in a patient with HOS. We further document the challenges faced addressing the side effects of the chemotherapeutic regimen for a patient with congenital conduction anomalies.

CASE REPORT

A 12-year-old female with clinically diagnosed HOS status postatrial septal defect and ventricular septal defect repair at 3 months of life and known first-degree heart block was admitted to Rush University Medical Center for newly diagnosed B-ALL. She presented to Pediatric Cardiology Clinic for transient, position-dependent presyncopal episodes over a 2-month period. A 30-day event monitor was placed and did not reveal any heart block during a syncopal episode. During this period, she also presented to her primary care provider for pallor. A complete blood count revealed thrombocytopenia and anemia. The patient was subsequently admitted due to concern for leukemia on further workup [Table 1]. Her physical examination was remarkable for bilateral submandibular and anterior cervical lymphadenopathy, a systolic murmur, hepatosplenomegaly, pallor, and absence of thumbs bilaterally.

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On the day of admission, hospital day 0 (HD0), a baseline echocardiogram revealed normal function and no residual septal defects. A baseline electrocardiogram (ECG) demonstrated a normal sinus rhythm with first-degree AV block and a QTc of 479 ms [Figure 1a]. On HD1, a bone marrow biopsy confirmed the diagnosis of B-ALL. On HD3, intrathecal cytarabine was administered for day of induction 1 (DOI#1). She was given a single dose of intravenous vincristine and daunorubicin followed by oral prednisone after recovery from anesthesia. During DOI#2, she was noted to have a heart rate (HR) between 40 and 50 bpm even while awake after the fourth dose of steroid. She was asymptomatic with normal orthostatic blood pressure measurements, normal electrolytes, and a 12-lead ECG with sinus bradycardia and first-degree AV block [Figure 1b]. A 24-h Holter monitor was placed on DOI#3 and revealed an average HR of 50 bpm (range: 36–81 bpm). The patient experienced significant nausea during induction that was only responsive to ondansetron. She underwent continuous monitoring with daily ECGs without issue. She was asymptomatic from the bradycardia throughout the hospitalization and was discharged on DOI#5 with a HR 56 bpm. At follow-up visits, her HR range was predominantly within normal limits. On subsequent admissions, the lowest HR documented was 42 bpm with HR predominantly above 50 bpm.

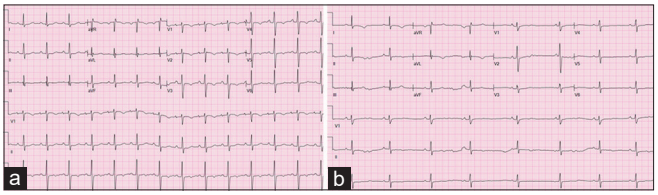

Figure 1: (a) Baseline electrocardiogram on the day of admission demonstrating a prolonged PR interval and mild QTc prolongation. (b) Electrocardiogram obtained during bradycardic episodes demonstrating sinus bradycardia, prolonged PR interval, and no QTc prolongation

Table 1: Baseline characteristics and laboratories at the time of admission

Baseline characteristics	Result
Height	154.7 cm
Weight	52.1 kg
BSA	1.5 m^2
WBC	14.9 K/μL
Hemoglobin	6.7 g/dL
Platelet	68 K/μL
Neutrophil	940 K/μL
LDH	304 U/L
Uric acid	6.7 mg/dL
Folic acid	5.2 ng/mL
Ferritin	490 ng/mL
Chest X-ray	normal
PR interval	192 ms
QT/QTc	406 ms/477 ms

BSA: Body surface area, WBC: White blood cell, K: 1000, U: Units, LDH: Lactate dehydrogenase

DISCUSSION

While leukemia is the most common form of cancer in pediatric patients, no cases have been documented in a patient with HOS.[2] To the best of our knowledge, HOS in association with malignancy is rare, with six cases documented in the literature [Table 2].[3-8] From these documented cases, only Yoshihara *et al.* reported challenges and limitations before chemotherapy treatment due to concern for side effects in the context of acute heart failure.

Our patient experienced bradycardia on DOI#2. We postulated that her bradycardia may have been due to three potential etiologies: first, this was a natural progression of her underlying conduction defect; second, this was an acute change secondary to the oncologic burden; and third, this was chemotherapy-related, specifically steroid-associated bradycardia. The first two

Table 2: The case reports previously published on patients with Holt-Oram syndrome and identified malignancy

Age/sex	Malignancy	Skeletal anomalies	Heart defect	References
16 years/ female	Adenocarcinoma	Short upper appendages with small scapulae, humeri, radii, and phalanges	Atrial septal defect*	Rabinowitz *et al.* 1971
24 years/male	Lymphosarcoma	Left arm 10 cm shorter than the right. Deformity of the end of the humerus with the congenital subluxation of the elbow; fusion of metacarpal bones; absence of left thumb, fifth finger, first and fifth metacarpal bones	Atrial septal defect	Nik-Akhtar *et al.* 1974
23 years/ female	Pheochromocytoma	Bilateral agenesis of radial bone and first finger	Dextrocardia, single ventricle, pulmonary atresia	Yoshihara *et al.* 2008
41 years/male	Adenocarcinoma	Bilateral radial foreshortening, triphalangeal thumbs, digit aplasia	Not reported	Aherne *et al.* 2013
7 months/ female	Nephroblastoma	Bilateral absence of the radial bones; deformed, shortened ulna bones; and bony ankylosis of the elbows	Ventricular septal defect	Usang *et al.* 2016
31 years/male	Squamous cell carcinoma	Bilateral thumb anomalies	Atrial septal defect	Rana *et al.* 2017

The patient HOS and malignancy characteristics are provided when available. *Patient refused catheterization but had findings consistent with ASD. HOS: Holt-Oram syndrome, ASD: Atrial septal defect

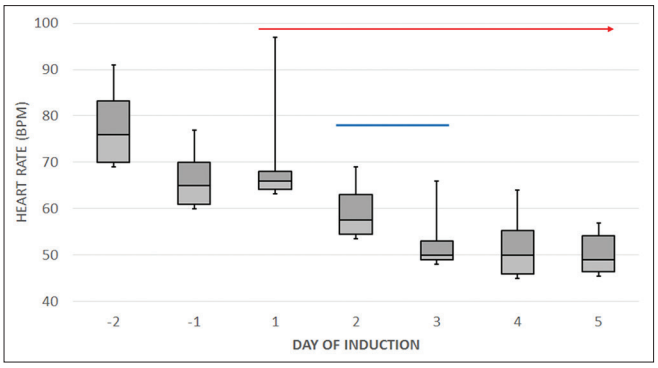

Figure 2: Box plot demonstrating heart rate trend during hospitalization. The y-axis is heart rate and x-axis is time based on the day of chemotherapy induction. Horizontal red line indicates steroid administration. Horizontal blue line encompasses the time period when Holter monitor was completed

theories were contradicted by the fact that the patient's resting HR during the portion of the admission before DOI#1 was within the normal limits (average HR 68 with range 61–97 bpm). This differed significantly from the 24-h Holter monitor completed on DOI#3 (average HR 50 with range 36–81 bpm). Moreover, the acute onset of the bradycardia without symptoms [Figure 2] and the lack of return at follow-up visitsfurther support the theory that this was a response to the initiation of potent steroids. Another potential cause of bradycardia could be attributed to the patient's hypervolemic state while undergoing hydration therapy. The patient received other medications during this time; however, the incidence of bradycardia occurred long after their administration.

Corticosteroid-associated bradycardia is a physiologic response first noted in patients with rheumatoid arthritis receiving pulse intravenous methylprednisolone.[9] There are numerous reports of patients developing this response to receiving pulse steroids for rheumatologic as well as oncologic conditions with one report demonstrating a nadir after 5–10 doses of steroids.[10-12] We speculate that the initiation of high-dose steroids may modulate a bradycardic response through androgen receptors that are not sustained during prolonged exposure. However, further research is needed to elucidate the mechanism. We further summarize that her presyncopal episodes before admission were vasovagal in nature confounded by anemia due to B-ALL.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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