Testicular failure following severe diabetic ketoacidosis complicated by hypotensive shock

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Introduction

Acquired primary gonadal failure in adolescents and young men is rare. The differential diagnoses includes infections, autoimmune orchitis, testicular tumors, recurrent testicular torsion or trauma, chemotherapy, radiation treatment and, in rare cases, alcohol abuse (See Table 1) [1]. Signs and symptoms of primary gonadal failure depend on the time of diagnosis. Neonates will present with microphallus, absent testicles, and underdeveloped scrotum. In the peripubertal/pubertal period, a child fail to progress in puberty as evidenced by lack of testicular enlargement, poor pubertal height gain, and low testosterone levels in conjunction with elevated gonadotropins. For some individuals, particularly in the case of Klinefelter syndrome which affects 1:600 men, there is usually some degree of testicular enlargement and testosterone production. However, hypogonadism and infertility due to sertoli cell failure are evident. Here, we report a case of an adolescent with evidence late gonadal pubertal staging who acquired primary gonadal failure shortly after he presented with severe diabetic ketoacidosis (DKA) at the onset of his diagnosis of diabetes. The clinical scenario presented is consistent with hypoperfusion damage to the testes secondary to shock.

Case Presentation

A 14-year-old Caucasian boy with no significant past medical history presented to the emergency department when his mother was unable to wake him up. The family reported a 3 day history of flu-like symptoms with polyuria and polydipsia but no vomiting. On exam, the patient was unresponsive but had no localizing neurological findings. Physical exam was remarkable for Kussmaul breathing, hypotension, and poor perfusion. Exam by the consulting endocrine team at presentation documented normal body mass index, no acanthosis, and sexual maturity staging of Tanner 4 for pubic hair with testicular volume of 15 mL bilaterally. The patient was diagnosed with severe DKA based on labs which showed pH 6.89, bicarbonate 4.5 mmol/L, blood glucose 1493 mg/dL, and ketonuria. He had acute renal failure with initial blood urea nitrogen (BUN) of 59 and serum creatinine 3.4 mg/dL. Fluid resuscitation and insulin infusion were initiated. The patient was transferred to the pediatric intensive care unit (PICU) for further management. Additional labs drawn at presentation are shown in Table 2.

While in the PICU, in spite of biochemical resolution of DKA, the patient had persistent hypotension and developed multi-system organ failure. He had a normal serum cortisol level in response to a 1 mcg cosyntropin...
Table 1. Differential diagnoses for primary testicular failure.

Klinefelter syndrome
Viral orchitis (e.g., Mumps, Coxsackie virus)
Autoimmune orchitis
Isolated autoimmune orchitis
Autoimmune polyglandular syndromes
Vascular insult
Recurrent testicular torsion
Ischemic injury following systemic hypotension
Testicular trauma
Testicular tumor
Cancer chemotherapy (radiation, alkylating agents)
Anorchia (congenital or postsurgical)
Idiopathic

Table 2. Labs at presentation.

| Lab test          | Patient value | Reference range |
|-------------------|---------------|-----------------|
| pH                | 6.89          | 7.35 – 7.45     |
| Bicarbonate       | 4.5 mmol/L    | 20 – 30 mmol/L  |
| Blood glucose     | 1493 mg/dL    | Fasting <100 mg/dL, Postprandial <140 mg/dL |
| BUN – Blood urea nitrogen | 59 mg/dL | 5 – 19 mg/dL |
| Creatinine        | 3.4 mg/dL     | 0.4 – 0.9 mg/dL |
| HbA1c             | 11.6%         | <5.7%           |
| C-peptide         | 0.4 ng/mL     | 0.8 – 6.0 ng/mL |
| Islet autoantibodies | 10          | <5             |
| GAD-65 autoantibodies | 7.1 unit/mL | <1.1 unit/mL |
| TSH               | 4.450 mcUnit/mL | 0.400 – 6.000 mcUnit/mL |
| Free T4           | 0.69 ng/dL    | 0.80 – 1.80 ng/dL |
| Tissue transglutaminase antibodies | 4.0 units | 0.0 – 20.0 units |
| IgA               | 246.0 mg/dL   | 70.0 – 390.0 mg/dL |

stimulation test performed on day 3 of admission (baseline 15 mcg/dL, t = 60 min 25 mcg/dL; 4–20 mcg/dL), and blood cultures drawn at presentation were negative. Brain imaging did not disclose cerebral edema. Management included mechanical ventilation, both conventional (for 10 days) and high-frequency oscillatory (for 5 days), pressor therapy, and additional supportive care. After 25 days in the PICU, the patient improved and was discharged on multiple daily injection insulin therapy.

At his first diabetes outpatient clinic visit 3 months after his initial diagnosis, the patient had no complaints of poor energy. On physical exam, testicular volumes were 2 mL bilaterally with adult penile size and pubic hair Tanner stage 4. Laboratory studies to assess this change in testicular volume showed 46, XY karyotype, testosterone level of 205 ng/dL (Genital stage Tanner 3 – Tanner 4, drawn at 7 am), elevated gonadotropins (luteinizing hormone (LH) 15.02 miU/mL (0.29–4.77); follicle-stimulating hormone (FSH) 17.85 miU/mL (0.40–7.40)), and low inhibin B (<10 pg/mL). Bone age was 14 years, corresponded to chronological age. Based on these finding, a diagnosis of primary gonadal failure was made, and topical testosterone replacement therapy was started.

Discussion

We present an unusual case of a young man who developed primary gonadal failure coincident with his presentation of new onset diabetes. Differential diagnoses for hypergonadotropic hypogonadism are presented in Table 1. While individuals with Klinefelter syndrome (47, XXY) are at increased risk for Type 1 diabetes, the normal male karyotype rules out this diagnosis in our patient [2]. In addition, the unique finding of testicular volume regression from initial presentation is more consistent with an anatomical insult to the gonads. Viral orchitis is usually accompanied by testicular pain, which was not elicited at presentation [3, 4]. However, this diagnosis cannot be completely ruled out in our patient given his altered mental status during the illness, which did not allow for localized pain assessment. Autoimmune orchitis may be isolated or part of autoimmune polyglandular syndromes (APS). Autoimmune orchitis usually presents with signs of testicular inflammation. Initially, gonadotropin levels may be normal. Over time, LH and FSH will both rise indicating Leydig cell failure with subsequent low testosterone levels, and Sertoli cell failure which will be reflected in low inhibin B levels and impaired spermatogenesis [5]. Gonadal failure is rare in APS (5%), and it is unlikely that it would copresent with only Type 1 diabetes, the only other autoimmune diagnosis in our patient [6].

Sheehan syndrome occurs in individuals who suffer a severe hypotensive event. The syndrome is characterized by development of pituitary hypofunction, which may result in gonadal failure. However, gonadotropins will be low, indicating central hypogonadism, rather than elevated, as described in our patient.

The clinical scenario presented is most consistent with a direct vascular insult to the testes which would explain the abrupt regression in testicular size from the initial presentation. The testes receive blood supply through the testicular artery. Interruption of this arterial supply via spermatic cord torsion or disruption of blood flow secondary to shock could lead to testicular damage and subsequent primary gonadal failure. We suggest that the final diagnosis was ischemic testicular injury secondary to hypovolemic shock.
Conclusion

The finding of testicular regression following an episode of severe hypotension is what prompted the biochemical evaluation for our patient. This case highlights the importance of performing comprehensive physical examinations including genital exam in both inpatient and outpatient settings. Without initial complete physical exam on presentation and follow-up exam, testicular dysfunction would not have been identified in a timely manner, and this patient would likely have developed signs and symptoms of androgen deficiency.

Consent

Patient and parents gave their informed written consent.

Conflict of Interest

None declared.

References

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