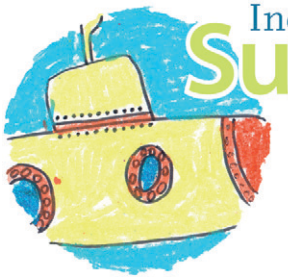

Index of Suspicion

2 Generalized Anasarca in 15-year-old Girl With Type 1 Diabetes Mellitus

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PRESENTATION

A 15-year-old girl with a history of poorly controlled type 1 diabetes mellitus presents to the emergency department with a 4-day history of generalized swelling. She initially noticed bilateral lower extremity edema and right-sided facial swelling that subsequently progressed to include both sides of her face, her abdomen, pelvis, and labia. She also reports a 9-lb (3.54-kg) weight gain. She denies pain, fever, vomiting, loose stools, chest pain, or shortness of breath. Current medications include insulin glargine and insulin aspart. She has only become compliant with this therapy in the past week.

On physical examination, the teen's weight is 51 kg (41st percentile), height is 155 cm (13th percentile), and body mass index is 20.1 (54th percentile). Her vital signs are within normal limits. She is in no acute distress. She has mild facial edema, moderate abdominal distention without fluid wave, mild right upper quadrant tenderness, and 2+ pitting edema of the ankles bilaterally. Cardiac, pulmonary, and neurologic examination results are normal.

Findings on laboratory studies, including complete blood cell count, comprehensive metabolic panel, amylase, and lipase, are within normal limits. Bedside glucose measures 75 mg/dL (4.2 mmol/L). Albumin is mildly low at 3.3 g/dL (33 g/L). Urinalysis is positive for glucose greater than 1000 mg/dL (>55.5 mmol/L), but negative for ketones, blood, or protein. Computed tomography scan of the abdomen, pelvis, and chest; inferior vena cava ultrasonography; and chest radiograph demonstrate no clot or other acute pathology. Review of the data and consultant discussion leads to the diagnosis.

DISCUSSION

The patient was admitted to the hospital for observation and further studies. On admission, she was placed on a fluid- and sodium-restricted diet and her home insulin regimen was continued. Further studies were obtained to rule out thrombotic, inflammatory, renal, or cardiac causes of her anasarca. A prothrombin time, partial thromboplastin time, and international normalized ratio were within normal limits. An erythrocyte sedimentation rate was obtained to screen for an inflammatory condition. Complement C3, C4, and CH50 total complement tests were obtained to evaluate for immune-mediated renal pathology. Finally,

echocardiography was performed to evaluate for a cardiac abnormality. Results from all of these studies were within normal limits and did not reveal the cause for her edema.

Pediatric endocrinology was consulted to assist in the evaluation and management. A detailed review of her outpatient diabetes management history and recent laboratory studies, including normal thyroid tests, was undertaken. Based on these data and those obtained during this hospitalization, the patient was diagnosed with insulin-induced edema. She was discharged home on a sodium-restricted diet with endocrine follow-up appointment. Her anasarca resolved over the next few weeks.

Differential Diagnosis

Insulin-induced edema is a diagnosis of exclusion. Evaluation should focus on the organ systems, including cardiac, renal, hematologic, hepatic, endocrine, and immunogenic, in which edema would herald a life-threatening condition. Cardiac evaluation should initially focus on physical examination findings suggestive of congestive heart failure. Renal evaluation should encompass urinalysis, serum blood urea nitrogen, and creatinine to assess for glomerulonephritis, glomerulonephrosis, or acute tubular necrosis. Substantial edema, particularly abdominal and pedal edema, necessitates examination of liver enzymes and coagulation studies to determine if hepatic injury is present. Hematologic evaluation focuses on finding a potential thrombus and might include coagulation studies and imagining studies to look for distal venous thrombosis, portal vein thrombosis, or cardiac thrombus. Severe hypothyroidism can also cause edema, necessitating thyroid function studies. Because a generalized inflammatory condition could affect multiple organ systems, an inflammatory process must be excluded. Once the clinician has ruled out these serious possibilities, insulin-induced edema can be considered.

The Condition

Insulin-induced edema is a rare adverse event associated with the initiation or intensification of insulin treatment. It primarily occurs in patients with type 1 diabetes but has also been noted in those who have type 2 diabetes. The typical patient is an underweight female who presents with mild-to-moderate generalized edema and substantial weight gain associated with the initiation or intensification of insulin therapy. The pathogenesis of the condition is primarily related to the edematogenic properties of insulin and the nutritionally deficient state of the patient, but it also can be related to mitochondrial mutations in select populations with type 2 diabetes.

Insulin can cause edema through two principal mechanisms: sodium retention and increased capillary permeability. Sodium retention occurs through insulin's action on the kidney. Insulin has a primary action on the tubules of the kidney that increases sodium reabsorption. Insulin also has secondary effects that increase sodium retention. More aggressive efforts to improve glycemic control with insulin can result in hypoglycemia, which can cause release of cortisol, renin, aldosterone, and vasopressin. These hormones have a net effect of increasing sodium retention and decreasing diuresis. Insulin also increases capillary permeability. This results in the escape of albumin from the intravascular space into the interstitial space, which causes net fluid movement into the tissues, resulting in edema.

The nutritional status of the patient also plays a major role in insulin-induced edema. Most patients with insulin-induced edema are underweight and can be considered as nutritionally deficient. They exhibit very high glucagon and low insulin values. High glucagon concentrations are associated with natriuresis. When insulin is reintroduced, the sudden decrease in glucagon and concomitant increase in insulin causes cessation of natriuresis and subsequent sodium retention. This is very similar to the edema that can be seen with the refeeding syndrome in malnourished patients.

Management

Management of insulin-induced edema is based on the severity of symptoms. Sodium and fluid restriction is the mainstay of acute management. However, loop diuretics can be considered for a patient who is experiencing significant symptoms as a result of the edema. Eventually, adequate glycemic control removes the underlying malnourished state that predisposed the patient to this condition. The long-term prognosis is good and the edema generally resolves over the course of a few weeks.

Lessons for the Clinician

- Insulin-induced edema is a condition caused by poor glycemic control inducing a nutritionally deficient state that results in generalized edema with the reintroduction or intensification of insulin.
- The diagnosis is one of exclusion, but a history of initiation of insulin therapy following newly diagnosed or poorly controlled type 1 diabetes mellitus suggests the diagnosis.
- Management of insulin-induced edema includes sodium and fluid restriction. Diuretics should be considered in severe cases. The re-establishment of a properly nourished state and glycemic control is the key to management.

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