

Insulin-Dependent Diabetes Mellitus in 2 Male African American Children After Kawasaki Disease

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ABSTRACT. Two children with insulin-dependent diabetes mellitus (IDDM) presented with diabetic ketoacidosis within 4 months of being diagnosed with Kawasaki disease (KD). Both patients were African American males younger than 4 years of age. Immune markers associated with the autoimmune cause of diabetes were not detectable in these patients at the time of diagnosis with IDDM. In 1 patient, the immune markers were repeated 6 months after diagnosis but remained negative. Both patients currently require ~1 unit of insulin/kg/d. Occurrence of IDDM after KD is rare; we could find no such reports in the English literature. The cause of diabetes in these 2 patients remains elusive, as does the cause of KD. *Pediatrics* 2002;110(2). URL: <http://www.pediatrics.org/cgi/content/full/110/2/e27>; *insulin-dependent diabetes mellitus, Kawasaki disease, diabetic ketoacidosis*.

ABBREVIATIONS. IDDM, insulin-dependent diabetes mellitus; KD, Kawasaki disease; IgA, immunoglobulin A; IVIG, intravenous γ globulin; ICA, islet cell antibody; GAD, glutamic acid decarboxylase; DKA, diabetic ketoacidosis.

In the vast majority of cases involving children and adolescents, insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease possibly triggered by a viral infection in a genetically susceptible individual.^{1,2} Kawasaki disease (KD) is a multisystem disease believed to be caused by a yet unidentified agent.^{3,4} Although at the present time there have been no published reports to link KD with IDDM, there is evidence to support pancreatic involvement in KD. In 1987, Stoler and collaborators⁵ reported 2 cases of pancreatitis in children shortly after they developed KD. Both patients improved without significant sequelae. Lanting et al⁶ described a 5½-year-old child who presented with pancreatitis 4 days before developing classic symptoms of KD.⁶ Pancreatitis associated with KD has also been reported in an adult patient.⁷

IDDM as a sequela of KD is probably rare and to our knowledge has not been reported. In a recently published study⁸ to evaluate the presence of increased immunoglobulin A (IgA) plasma cells at mucosal sites in patients who had died from complica-

tions of KD, pancreatic involvement was observed. All 14 patients included in the study were found to have periductal infiltration of IgA plasma cells. Some also had fibrotic changes. However, the investigators did not report a significant involvement in β cells of the pancreas. We report 2 patients in whom IDDM was temporally related to the development of KD.

CASE REPORTS

Case 1

A 3-year, 6-month-old African American male presented with fever ranging from 102°F to 104°F 5 days before admission. Clinical findings included diffuse oropharyngeal erythema with oral mucositis and bilateral bulbar nonexudative conjunctivitis. He had edema of his palms and soles and a diffuse maculopapular rash, which developed 48 hours after his admission. There was a 3.5-cm, palpable lymph node in the right-side medial anterior cervical chain; the node was firm, enlarged, and nontender. His initial laboratory findings included a sedimentation rate of 70 mm hour and an elevated blood level of C-reactive protein. In addition, thrombocytosis was observed during the second week of illness with a platelet count of 650 000. A diagnosis of KD was made, and the patient was treated with aspirin and intravenous γ globulin (IVIG). His fever resolved within 3 days. An echocardiogram did not reveal any coronary artery involvement, and he was discharged with outpatient follow-up.

Four months after the diagnosis of KD, the patient was evaluated for polyuria, polydipsia, weight loss, vomiting, and weakness. Symptoms of polyuria and polydipsia had been noted for ~3 weeks before this visit. His heart rate was 114 beats/min, respiratory rate 30/min with Kussmaul's breathing, rectal temperature 99.8°F, blood pressure 100/62 mm Hg, weight 13.4 kg, and height 99 cm. Physical examination revealed moderate dehydration, and the patient was lethargic but oriented. There was no focus of infection. His system review and physical examination were otherwise unremarkable.

Pertinent laboratory findings included blood glucose of 532 mg/dL and venous pH of 7.1. Urinalysis revealed a large amount of glucose and ketones. Additional tests included islet cell antibody (ICA), glutamic acid decarboxylase (GAD), and serum C-peptide (Table 1). The patient responded satisfactorily to supportive treatment with fluid and insulin infusion. He was discharged on treatment with intermediate and short-acting insulin before breakfast and supper. In the 3 years since diagnosis, he has had 2 more admissions with diabetic ketoacidosis (DKA). At present he is receiving 1 unit of insulin/kg/d with unsatisfactory control. His last hemoglobin A1C was 9.5%. Tests for immune markers (ICA, GAD) repeated 6 months after the diagnosis of IDDM were also negative.

Case 2

A 2-year, 5-month-old African American male was admitted to the hospital with major clinical and laboratory criteria consistent with the diagnosis of KD. He responded satisfactorily to treatment with IVIG and aspirin. The child defervesced after a 48-hour infusion of IVIG. An echocardiogram was performed with no evidence of coronary artery involvement. This patient presented 3½ months after being diagnosed with KD with a history of vomiting, severe dehydration, lethargy, and weight loss. The patient's mother gave a history of frequent wet diapers and poly-

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TABLE 1.

Patient Age at Diagnosis	Blood Glucose mg/dL	Venous pH	C-Peptide (Reference Range 0.9–3.9 ng/mL)	GAD (Reference Range 0–1.45 U/mL)	ICA (Reference Range <1:4)
Patient 1 3 y 6 mo	532	7.10	<0.1	<1	<1:4
Patient 2 2 y 8 mo	598	7.09	<0.1	<1	<1:4

dipsia for 10 days or more. At admission the patient had a rectal temperature of 100°F, blood pressure of 90/50, and pulse of 130/min, and was tachypneic with Kussmaul's breathing. He was estimated to be >10% dehydrated and was lethargic, but responded to verbal commands. The physical examination was otherwise unremarkable. Pertinent laboratory findings included blood glucose of 598 mg/dL and venous pH of 7.09, and the boy's urine contained a large amount of glucose and ketones. Additional laboratory tests for immune markers for type I diabetes and C-peptide were obtained (Table 1).

The patient was admitted for DKA management and responded well to intravenous fluids and insulin therapy. He was discharged from the hospital with intermediate and short-acting insulin before breakfast and supper. He was started with 0.8 units of insulin/kg/d with unsatisfactory control of blood glucose. Eventually insulin was increased to 1 unit/kg/d. Blood glucose continued to be erratic, ranging mostly between 200 and 350 mg/dL, and hemoglobin A1C ranged from 8.7% to 10.4%. After 18 months under our care, the family moved from our area.

DISCUSSION

KD is an acute, multisystem inflammatory disease that primarily affects infants and young children.^{3,4} Since the initial report of KD, knowledge has proliferated about its clinical description, pathogenesis, diagnostic criteria, and therapy. Clinical and epidemiologic data support an infectious cause of KD, but the cause and pathogenesis of the illness remain elusive.^{3,4} Although the cardiovascular pathology of KD has been well described,^{9,10} much less information exists in the English-language literature regarding pathologic changes in nonvascular tissues.⁸ Multiple systems are involved in KD, but to our knowledge the occurrence of IDDM has not been reported.

Both patients in this report fulfilled the clinical and laboratory diagnostic criteria of KD. Fever deferred within 72 hours after the administration of recommended doses of IVIG. Within 4 months of diagnosis of KD, both patients presented with DKA. Neither of these patients had a family history of type I diabetes. The first patient has had 2 admissions to the hospital for DKA since his diagnosis, indicating almost total lack of insulin production. Additional common characteristics between the 2 included race and gender. Neither patient went through a honeymoon phase. Immune markers for type I diabetes were negative with almost undetectable levels of C-peptide in both patients at the time of DKA. A repeat evaluation of immune markers was performed in the first patient 6 months after the diagnosis of diabetes, but the results remained negative with undetectable serum C-peptide levels.

The cause of diabetes in these 2 patients remains obscure. Clinical and biochemical evidence of pan-

creatitis has been reported with KD, and they usually resolve within 6 to 8 weeks.^{5,8} However, it is highly unlikely that pancreatitis caused diabetes in these patients.

In their series of 14 patients, Rowley et al⁸ observed and demonstrated pancreatic infiltration of IgA and plasma cells in periductular distribution. Five of the 14 patients showed extension of IgA and plasma cell infiltration into the pancreatic parenchyma, all of which showed acinar dropout and fibrosis, but the islet cells were not affected. Therefore, the above process, where β cells are spared, is also unlikely to be an etiologic factor in the pathogenesis of diabetes. The sample in this study was relatively small and may not have reflected in its entirety the pancreatic pathologic changes associated with KD. For that reason, additional studies would be needed to rule out the involvement of β cells in the development of this systemic vasculitis.

Although immune markers were absent in both of our patients, an immune-mediated process (type I diabetes mellitus) cannot be excluded completely. Only ~80% of individuals will be positive for ICA and/or GAD at the time of diagnosis.^{1,11} Documentation of typical HLA typing in the absence of immune markers would have been helpful in these patients; however, it was not performed. IDDM has been linked to infection with "diabetogenic viruses," which may trigger an autoimmune process or may destroy β cells by direct cytotoxic and cytopathic effects.^{1,11} It is presumed by many that KD may be caused by an infectious agent.^{3,4} If so, it is possible that the same agent that caused KD may have a direct cytotoxic and cytopathic effect on β cells of the pancreas in genetically susceptible individuals, resulting in complete destruction of those cells within a short period. Neither of our patients went through a honeymoon phase, which is usually common in this age group with autoimmune diabetes, further suggesting a rapid total destruction of β cells. Both patients required a progressive increase of insulin dose to control their hyperglycemia from their time of discharge. Therefore, the process may not be immune-mediated, explaining the negative immune marker for both patients.

The cause of IDDM in our patients remains elusive like the cause of KD. One may argue that the development of diabetes in these 2 patients is purely coincidental. This is certainly possible, but it is also hard to ignore the possibility of KD as an implicating factor, given the known multisystem involvement with this condition. We believe diabetes mellitus in

these 2 children may have been a sequela of KD. There may be other isolated cases like ours that remain unreported. Additional studies are needed to determine whether an association exists between KD and the development of IDDM.

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