

Case Report Of A Child With Recently Diagnosed Diabetes Mellitus Type 1 And Subsequent Systemic Arthritis

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Abstract

"Clustering" of autoimmune disorders is relatively common. Reports exist of concomitant insulin-dependent diabetes mellitus (DM1) and juvenile idiopathic arthritis (JIA). However there are few reports about coexistence of DM1 and the systemic subtype of JIA (sJIA), and even fewer documenting the chronological onset of DM1 before sJIA. In most reports, DM1 developed after therapy for preexisting sJIA. There is debate about whether those therapies played a causative role in the manifestation of DM1. Herein we describe an 11-year old male not receiving any such therapy who was diagnosed with DM1 one month prior to receiving a second diagnosis of sJIA. His diabetes necessitated an early taper of prednisone, and he was started on a regimen of daily anakinra (Interleukin-1 blocker). Afterwards, the patient experienced breakthrough inflammatory symptoms. He restarted a progressively lower dose of oral prednisone, which controlled his symptoms. In an effort to understand the rare instance of encountering these two diseases in one patient, we undertook a literature search to examine the possibility of a common etiology, with special focus on variations along the inflammatory cascade of the immune system, including the alleles encoding perforin and interleukin-6 (IL-6).

INTRODUCTION

DM1 has an incidence of approximately 17/100,000 in the United States and is highest in the 10-14 year old age group of most populations¹. There is a strong genetic variable, though the precise mechanism by which the immune system becomes dysfunctional has not been elucidated. One of the best-studied theories is that variations in the major histocompatibility complex (MHC) molecules, including the DR3 and DR4 alleles, predispose to beta cell dysfunction in the pancreas. Currently the best long-term treatment is to replace the endogenous insulin not being produced by the pancreas with subcutaneous exogenous insulin.

Systemic-onset juvenile idiopathic arthritis, classified as systemic arthritis under the International League of Associations for Rheumatology criteria², has an incidence between 1/10,000 and 5/10,000 and is most commonly diagnosed at age 1-2 years³. It is thought to emerge from a combination of environmental factors and genetic predisposition. However there is little association with MHC in sJIA as there is in the other forms of juvenile idiopathic arthritis⁴. Treatment can include non-steroidal anti-inflammatory medications, interleukin-1 and -6 (IL-1 and IL-6) inhibitors, tumor necrosis factor (TNF) blockers,

corticosteroids, and disease-modifying antirheumatic drugs like cyclosporine.

Given the lack of extensive data on patients with both DM1 and sJIA, this literature search focused on documented allele variants that are present in both diseases.

PATIENT PRESENTATION

A previously healthy 11 year old male with vomiting, diarrhea, and blood glucose of 800 mg/dl was admitted to a pediatric intensive care unit at an outside hospital and diagnosed with DM1. The patient was eventually discharged on a sliding scale insulin regimen. At the time of discharge, the patient had an urticarial, erythematous rash in the area of his right elbow which was attributed to the adhesive from his IV.

During the following days the rash persisted and spread throughout his body. After one week he developed daily fevers reaching 39.4 degrees Celsius that peaked during the afternoons and evenings. The rash would get worse with the fevers. He also complained of pain and swelling in his knees, hips, ankles, toes, and elbows. The patient's mother noticed swollen lymph nodes. The fevers lingered despite temporary relief with ibuprofen recommended by a pediatrician. After

two weeks of no improvement the patient was admitted to another hospital unable to walk due to pain in his joints.

Exam at the hospital revealed a blanchable, macular, erythematous rash over his face and torso, dermatographism, and arthritis in his elbows bilaterally and in his right index finger. There were no mucosal ulcers. Laboratory results showed a white blood cell count $16.6 \times 10^9/l$ with 62% neutrophils, hemoglobin 9.6 gm/dl, and normal platelet count $426 \times 10^9/l$. Blood glucose was 180 mg/dl. Erythrocyte sedimentation rate was 61 mm/h, C-reactive protein was 6.17 mg/l, fibrinogen was 528 mg/dl, d-dimer level was 1770 ng/ml, and ferritin was 1295 ng/ml. Total complement was normal at 129 mg/dl. Liver function and triglyceride laboratory results were normal. Infectious disease panels, blood culture, urine culture, and urinalysis were negative. Bone marrow aspirate showed no evidence of acute leukemia or non-hodgkin lymphoma. Abdominal ultrasound revealed mild hepatomegaly, and magnetic resonance imaging showed moderate effusion of his left elbow. During the hospital course the patient was diagnosed with systemic juvenile idiopathic arthritis (sJIA) based on history, physical exam, and laboratory findings. Family history was significant for a paternal cousin who required weekly injections for juvenile onset joint disease, and for another paternal cousin diagnosed with rheumatoid arthritis (RA) since age 20.

His discharge plan included oral prednisone 25 mg daily, to be tapered, and subcutaneous anakinra 100 mg daily. During the five days following his discharge, fever, rash, pain, morning stiffness, and swelling were absent, but the patient's blood glucose levels were consistently higher, sometimes reaching up to 600 mg/dl. On outpatient follow-up, prednisone was therefore decreased to 15 mg daily and subsequently tapered. Two weeks after discontinuing the prednisone, blood sugar levels were better controlled. However the patient continued to have breakthrough fever, rash, and ankle pain only partially controlled by anakinra. Prednisone was therefore re-started at 7.5 mg daily and was tapered slowly, while anakinra was increased. His blood glucose levels were better controlled with Novolog three times daily and Lantus one time nightly.

DISCUSSION

Although numerous papers have examined the association between non-systemic JIA and other autoimmune disorders, there is a paucity of work that documents the simultaneous existence of DM1 diagnosed before sJIA in a single patient.

One study reported seven children with both DM1 and JIA, but none of the subjects had sJIA⁵. Five of them received the DM1 diagnosis before the JIA diagnosis. Of the remaining two in whom JIA preceded DM1, one was already receiving corticosteroid therapy, known to cause hyperglycemia⁶. Five of the seven children were HLA-DR3 and DR4-positive, which are associated with both DM1 and non-systemic JIA. No such MHC association appears to exist for sJIA⁵.

In another case study of a patient with both DM1 and sJIA, the patient developed DM1 five months after anti-TNF etanercept therapy for sJIA⁷. The patient in question was glutamic acid decarboxylase antibody positive before etanercept therapy and therefore was likely to eventually develop DM1 even without intervention. It is well-recognized that the TNF molecule plays a pro-apoptotic role in the diabetogenic process⁸, but its effect on the destruction of pancreatic β cells seemingly depends on the stage of development at which the β cells are exposed to TNF⁹. Evidence in animal models has indicated a narrow therapeutic window for anti-TNF therapy, and it is possible that TNF suppression plays a key role in progression to DM⁷ by inducing autoimmunity in predisposed individuals¹⁰. Also in animal models, exposure to higher levels of TNF at younger ages seems to have a destructive effect on pancreatic beta cells, but it has a protective effect at older ages⁹. Therefore it is possible that the decreased level of TNF activity may have expedited the development of DM1 in the patient in this case study⁷.

Various inflammatory markers have been shown to be increased in sJIA, including Interleukin (IL)-12; IL-18; and chemokine ligands 3, 17, and 18¹¹. However, the most successful therapies against sJIA flares have been therapies targeting IL-1 and IL-6¹². IL-1 and IL-6 are known to be elevated in both sJIA and DM¹³. TNF and IL-1 (particularly IL-1 β) induce IL-6 production, which studies have shown to be both potentially protective and destructive for pancreatic beta cells¹³. Two major camps exist in the literature regarding how mutations in the IL-6 promoter region affect the development of sJIA and DM1. One case-control study¹⁴ and one cohort study³ illustrated that the G(-174)C substitution in a 5' flanking region of the IL-6 gene results in a G,C or G,G genotype, and the case-control study cited an increased frequency of the G allele among DM1 individuals compared to healthy controls¹⁴. The authors presented evidence that G,C and G,G genotypes are associated with higher levels of serum IL-6 and disruptions in insulin

sensitivity, while the C,C genotype has a strong association with low levels of IL-6 and increased insulin sensitivity. Additionally, patients with sJIA were shown to have a reduced frequency of the C,C genotype, and an increased frequency of the G,C genotype, with a noticeable functional increase in levels of IL-6 and possibly a predisposition to diabetes¹⁴. On the other side of the debate is research¹³ which shows that the C,C genotype is more common in children who experience the onset of DM1 at an earlier age. The G substitution is found in children who develop DM1 at a slightly older age, and only in association with high-producing TNF and IL-1 mutations, thereby probably allowing the increased levels of IL-6 to exert a protective measure over pancreatic cell destruction¹³. It is generally thought that IL-6 alone is insufficient to cause DM1, but its connection to other pro-inflammatory molecules such as TNF may play an as-of-yet unelucidated role¹⁵.

A slightly different approach to finding a link between sJIA and DM1 explores the concept that sJIA may be better understood as a macrophage-related disorder, along the same spectrum as hemophagocytic lymphohistiocytosis. In such disorders, natural killer cell (NKC) activity is consistently decreased. This may be due to mutations in the perforin-coding gene, or in the genes encoding the proteins that bring perforin to the cell surface⁴. The lack of perforin, a protein that enables cell lysis, at the cell surface prevents NKC from destroying antigen-presenting cells, which then continue secreting cytokines such as interferon alpha and granulocyte-macrophage colony-stimulating factor in the absence of acute infection. The resultant persistent macrophage activation produces high levels of inflammatory molecules such as TNF alpha and IL-6¹⁶. DM1 has similarly been proposed as a product of macrophage dysfunction, with considerable evidence in animal models that macrophage migration inhibitory factor plays a large role in the progression to DM1 and inhibits NKC^{17,18}. More importantly, DM1 may also be a consequence of a perforin mutation. One study found an DM1 patient with an unusual P477A variant perforin-encoding allele. NKC function was low in this patient, as it is in sJIA¹⁹. Not only was this mutation the only one of its kind out of a sample of 199 DM1 patients and 300 controls, but it was also one of the variants that did not require the presence of HLA-DR3 or DR4 to proceed to DM1. P477A could therefore represent a common ground for developing both sJIA and DM1, and its rarity in the population is consistent with this case report's assertion that the patient in question, with concomitant sJIA

and DM1, was an uncommon but significant finding.

CONCLUSIONS

Given the rarity of DM1 and sJIA individually, to find them together in one individual argues for the presence of a rare allelic variation in that individual. Although the patient in the case report was not tested for such a variation, a literature search proved that the explanation of this patient's concurrent diagnoses need not be left to coincidence. At least two genetic variations exist which can account for both disease presentations, and further research focusing on either the P477A variant of perforin or the inflammatory cascade surrounding the G(-174)C substitution for IL-6 may confirm an alternate pathway in the progression to other concomitant autoimmune disorders.

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