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Three-Month Retreatment with Cyclosporine A for a Relapse of Type 1 Diabetes Mellitus after 5 Years of Remission

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Abstract

Background: Type I Diabetes mellitus (T1D) results from genetic beta-cell disease that is triggered by autoimmunity. **The Case**: A 22-year-old man presented with escalating frequency of micturition for 1 week. He was dehydrated and laboratory tests revealed hyperglycemia (21 mmol/L), ketonemia, ketonuria and high Hemoglobin A1C (HA1c) that required resuscitation and insulin therapy. He did not have clinical, laboratory, radiological and serological evidence of recent drug use, chronic illness, autoimmune disease, infections and malignancy. He had similar presentations at the age of 16 years. At that time, he had 2 high insulin antibodies, viz, anti-insulin and anti-GAD yet negative islet cell antibody. Moreover, he had a normal level of C-peptide insulin. Hence, with such positive autoimmune picture and adequate beta-cell function, he was given a trial of Cyclosporine A (CsA) since it is a potent suppressor of T-helper lymphocytes and hence B-lymphocytes. It started at a dose of 100 mg twice daily for 3 months followed by 50 mg twice daily for a total of 1 year. Within 1 month; he did not require insulin-therapy and his insulin antibodies decreased to normal. Up to 5 years of follow-up; he remained in remission with normal HA1c. In his recent relapse of T1D, he did not have high insulin antibodies, as before, yet responded to 3-month re-treatment with CsA 100 mg twice daily and remained euglycemic for 1 year subsequently. **Conclusion**: T1D can be triggered by autoimmunity that may not be limited to the 3 insulin antibodies yet still amenable to early institution of 3-month CsA-therapy.

Keywords

Insulin, Antibodies, Diabetes Mellitus, Cyclosporine A, Treatment, Relapse

1. Introduction

Classically, Type 1 Diabetes mellitus (T1D) is associated with insulin deficiency due to autoimmune destruction of insulin-producing beta-cells in the islets of the pancreas [1]. It is the major cause of childhood diabetes mellitus and accounts for 10% of all cases of diabetes in the USA. In Europe, its incidence had increased in the past 15 years, by 70%, and its age of onset had decreased with doubling of cases in children under the age of 5 years [2]. Despite its refined insulin treatment; long-term complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease, are inevitable [3]. Hence, prevention of its progression is the ideal management. It was described after severe pancreatitis, malignancy, and drugs yet its major and primary etiology is genetic predisposition triggered by autoimmunity [4]. In this disorder, the goal of immunotherapy is threefold: 1) selective suppression of an ongoing autoimmunity, 2) reestablishment of long-term self-tolerance, and 3) preservation of acquired immunity. Multiple immunotherapeutic agents have been tried to prevent T1D, viz. Mycophenolate mofetil, Rituximab, Cytotoxic T-lymphocyte-associated protein 4 immunoglobulins, Anti-TNF agents, Anti-interleukin-1 drugs, Anti interleukin-1β, Anti-CD3 agents and specific immunomodulative strategies for Foxp3+ regulatory (Treg) cells [5]. However, those immunosuppressive agents were declared ineffective in treatment of T1D since they did not produce long-term self-tolerance and were associated with multiple long-term side effects. Previously, we reported our experience with a patient with recent-onset T1D that was associated with high anti-insulin and anti-GAD antibodies indicating autoimmune etiology and normal C-peptide insulin indicating adequate beta-cell reserve [6]. After his initial resuscitation, we treated him with Cyclosporine A (CsA) at a dose of 100 mg twice daily for 3 months with therapeutic blood level. He improved clinically and insulin therapy was discontinued 1 month later. To avoid future relapses, CsA therapy was reduced to 50 mg twice daily and maintained for a total of 1 year. He remained stable and without any medication for 5 years. However, his disease relapsed and in this case report, we describe its new features and our new protocol of management.

2. The Case

A 21-year-old man presented with progressive malaise and escalating frequency of micturition that became worse in the previous week. Six years ago, he had similar presentation that disclosed severe dehydration and multiple electrolytes imbalance that were associated with severe hyperglycemia (21 mmol/L), ketonemia and high hemoglobin A1C (HA1c) at 12%. Since he had (a) high anti-insulin and anti-GAD antibodies suggestive of acute autoimmune insulinitis, and (b) normal C-peptide insulin, he was treated with CsA 100 mg twice daily, which yielded therapeutic blood levels. Within 1 month, he improved clinically and did not require insulin. At the same time, his insulin antibodies decreased too normally. After 3 months, the dose of CsA was reduced to 50 mg twice daily and

maintained for a total of 1 year to avoid future disease-relapses. Subsequently, he remained stable and without treatment for 5 years till his recent presentation. Interestingly, on his routine testing, 4 months prior to his current relapse, he was well and with normal laboratory tests (Table 1). On his recent assessment, he was conscious and oriented yet was dehydrated with clear lungs, lack of oedema and postural hypotension to 90/60 mm Hg. He was afebrile with a body weight of 56 kg (BMI: 17.3 kg/m^2). Systemic examination did not show any abnormality. His initial laboratory investigations showed normal peripheral leukocytic and platelet counts. Hemoglobin was 17 g/L with normal MCV. Serum sugar was 21 mmol/L. Serum urea and creatinine were elevated at 12 mmol/L and 140 umol/L, respectively. Liver function was normal except for albumin at 55 g/L. Serum electrolytes showed hyponatremia, hypokalemia, hypophosphatemia and hypomagnesemia. He had severe metabolic acidosis with pH of 7.1 and bicarbonate at 8 mmol/L as well as ketonemia. Serum amylase and lipase were normal as well as fecal elastase level. Serum cholesterol was 8 mmol/L. TSH was normal. Serum ferritin was normal. Urine routine and microscopy showed 4 (+) glucose and ketones. Fasting C-peptide insulin was 0.8 nmol/L with normal level 0.26 - 1.27 nmol/L. Viral antibodies, autoimmune tests and tumor markers were negative. Antibodies to insulin, islet-cells and GAD were at normal levels. Chest x-ray, abdominal and pelvic ultrasound and CT were normal. He improved after rehydration, correction of electrolyte deficiencies and control of hyperglycemia with an insulin drip. Subsequently, he was discharged on Lantus 60 units pm and Novorapid 10, 18 and 10 units before respective meals. Since it was an acute relapse and previously had responded to CsA therapy; we elected to retreat with 100 mg twice daily yet only for 3 months. On weekly follow up; his insulin-requirement decreased with time and ultimately it was discontinued by 1 month later. By 3 months; he was well and with normal fasting serum glucose, bicarbonates, HA1c, C-peptide insulin and insulin autoantibodies. That remained stable up to 1 year of follow up (Table 1).

Table 1. Demographic characteristics and biochemical changes of a treated patient with relapses of type I diabetes mellitus.

		Time (months)								
		-72	-71	-60	-48	-4	0	1	3	12
Age, gender & race:	22 years, male, White									
Clinical data:										
Complaint	Polyurea & polydipsia	3(+)		(-)	(-)	(-)	3(+)	(-)	(-)	(-)
	Blood pressure (120-80 mm Hg)	90/60		120/80	120/80	120/80	90/60	120/80	120/80	120/80
	Body weight (Kg)	55		61	62	62	56	61	62	62
Laboratory tests*:										
Serum:										
	Glucose (fasting): (4-6 mmol/L)	14	5	5	20	5	21	5	5	6
	Creatinine: (60-120 umol/L)	156	61	60	62	62	140	62	63	59
	Bicarbonates: (22-28 mmol/L)	6	24	24	24	24	8	24	24	24
	Insulin antibodies: *	(+) (+) (-)	(-) (-) (-)	(-) (-) (-)	ND	ND	(-) (-) (-)	(-) (-) (-)	(-) (-) (-)	(-) (-) (-)
	C-peptide insulin:	Normal	Normal	Normal	ND	ND	Normal	Normal	Normal	Normal
	Hemoglobin A1c: (< 5.7%)	19	9	6	< 5.7	< 5.7	12	8	6	< 5.7
Urine Ketone										
	(-)	3(+)	(-)	(-)	(-)	(-)	3(+)	(-)	(-)	(-)
Drug therapy:										
	Insulin therapy									
	Cyclosporin A	100 mg X2		50 mg X2			100 mg X2			

* Insulin antibodies: (anti-insulin), (anti-GAD), (anti-islet cell)

3. Discussion

In T1D, β cell insulinitis and its subsequent loss have been attributed to both genetic predisposition and ill-defined autoimmune triggers. Nearly 50% were associated with HLA-DR3/4 DQ8 genotype, which has been shown to be highly associated with β-cell autoimmunity [7]. The latter results in chronic inflammatory response characterized by progressive infiltration of the pancreatic islets with various immune effectors [8]. In the nonobese diabetic mouse, a spontaneous model of T1D, islet infiltration is initiated, at an early age, by macrophages and dendritic cells, $CD4^+$ and $CD8^+$ T cells, and B cells. Initially, it doesn't alter β cell viability or function yet followed by a late preclinical stage with ill-defined qualitative changes in such islet infiltrate, which promotes β cell destruction and overt diabetes [9]. The catalysts/triggers of such late-transformation in predisposed subjects are ill-defined yet include viruses, viz. Coxsackie B4 [10]. On histopathology, pathogenic β cell-specific $CD4^+$ and $CD8^+$ Teff in non-obese mice and T1D humans typically exhibit a type 1 or T helper 1 phenotype marked by IFNγ production [11]. The first antibodies described in association with the development of T1DM were Islet Cell Autoantibodies (ICA). Subsequently, antibodies to insulin, Glutamic Acid Decarboxylase (GAA or GAD) and protein tyrosine phosphatase (IA2 or ICA512) have all been defined [2]. Studies have shown that these bodies are markers for identifying persons with increased risk for diabetes development [12]. In our patient, we elected to treat his autoimmune T1D with CsA since it is a potent inhibitor of Interleukins (IL), including IL-2, which is essential for the self-activation, proliferation and differentiation of T-helper lymphocytes. The latter are essential for activation of B-lymphocytes and hence antibody-production is blocked. It does not cause bone marrow suppression or impair leukocyte's phagocytic function [13]. Its previous initiation of CsA, at an early stage with adequate C-peptide insulin, led to both euglycemic status and suppression of autoantibody production which indicates its efficacy in prevention of D1T. At that time, he was treated with 100 mg of CsA twice daily for 3 months followed by 50 mg twice daily for another 9 months. His CsA levels were adequate (within therapeutic range) only during the first 3 months and we elected to continue with the subsequent subtherapeutic dose for a total of 12 months to avoid possible relapse and long-term side effects of CsA-induced interstitial fibrosis [14]. With that therapy, he remained well and in remission for 5 years. Hence, in his current relapse; we elected to retreat him with an adequate therapeutic dose of CsA yet for 3 months only. Despite lack of the 3 insulin autoantibodies, his disease remitted and the patient remained well up to 1 year of follow up. It should be noted that our patient did not have acute significant stress, infection and disease that may have raised his insulin requirements [15]. Moreover, his hyperglycemia persisted for months, prior to CsA therapy, as indicated by high HA1c. His impact of plain correction of hyperglycemia (glucose toxicity) with diet & insulin therapy leading to pancreatic rest (Honey moos state of T1D) is tentative yet the relapsing nature of his disease, severity, rapid response with complete cure of T1D and prolonged period

of remission (5 years) are more in favor of treatment of immune insult rather than glucose toxicity [16]. His acute presentation, persistent hyperglycemia and rapid response to CsA, excluded maturity onset diabetes (MODY) [17]. Moreover, the patient was and remained at a healthy BMI and his C-peptide insulin was not high, which excluded chronic insulin resistance [18]. Fortunately, he presented early with normal C-peptide insulin that indicated adequate insulin reserve and was amenable to cure if the culprit (autoimmunity) is removed.

4. Conclusion

T1D is a dormant genetic disorder that can be triggered by multiple autoimmune mechanisms with/without insulin antibody markers. Fortunately, early institution of CsA for a limited period of 3 months can abort its evolution and even future relapses.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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