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Case Series

Autoimmune conundrum in children with type 1 diabetes mellitus: a case series of uncommon associations

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder commonly associated with other autoimmune conditions, particularly autoimmune thyroid disease and celiac disease. However, involvement of non-classical organs such as the liver, hematologic system and parathyroid glands is uncommon in children and often under-recognized. We report three pediatric cases illustrating diverse autoimmune associations with T1DM. The first case is a 9-year-old boy with T1DM who after four months of T1DM diagnosis, developed recurrent jaundice, ascites and splenomegaly and was diagnosed with biopsy-proven autoimmune hepatitis. The second case is a 7-year-old girl with chronic immune thrombocytopenic purpura (ITP) from early childhood who subsequently developed T1DM 4 years later. The third case is an 8-year-old girl with T1DM who presented after two years with hypocalcemic tetany due to autoimmune hypoparathyroidism and recurrent mucocutaneous candidiasis, suggestive of an autoimmune polyglandular syndrome type 1–like phenotype. These cases highlight the expanding spectrum of autoimmune disorders associated with pediatric T1DM beyond classical endocrine conditions. Restricting evaluation to routine screening alone may result in delayed diagnosis and increased morbidity. Clinicians should maintain a high index of suspicion for atypical autoimmune manifestations in children with T1DM to enable early diagnosis, appropriate management and improved long-term outcomes.

Keywords: Diabetes mellitus type 1, Autoimmune polyendocrine syndromes, Hepatitis, Autoimmune, Purpura, Thrombocytopenic, Idiopathic, Hypoparathyroidism, Autoimmune diseases

INTRODUCTION

Autoimmunity is characterized by loss of immune tolerance, resulting in immune-mediated injury to self-tissues. Autoimmune diseases frequently occur in clusters due to immunological cross reactivity and shared genetic loci. Thus, the presence of one autoimmune disorder increases the risk of developing additional autoimmune conditions. Type 1 diabetes mellitus (T1DM) is one of the most common chronic autoimmune disorders encountered in paediatrics and results from immune-mediated destruction of pancreatic β-cells.[1,2] Autoimmune thyroid disease (AITD) and celiac disease are the most frequently associated autoimmune conditions in children with T1DM and are therefore routinely screened in clinical practice. AITD has been reported in approximately 17–30% of children with T1DM while celiac disease is detected in 4–10% of affected children.[1-3] These associations reflect a shared background of genetic susceptibility and immune

dysregulation. While much of the existing literature focuses on endocrine autoimmunity, increasing evidence suggests that immune involvement in T1DM may extend beyond classical endocrine organs, particularly in children.

Autoimmune hepatitis (AIH), immune thrombocytopenic purpura (ITP) and autoimmune hypoparathyroidism represent uncommon but clinically important autoimmune associations with T1DM. Pediatric literature describing these conditions in association with T1DM remains sparse and heterogeneous, resulting in limited consolidated clinical data and potential delays in recognition.[4-6] We describe three children with T1DM who developed autoimmune hepatitis, ITP and autoimmune hypoparathyroidism, respectively. These cases highlight the heterogeneous and evolving spectrum of autoimmune disease in pediatric T1DM and underscore the importance of maintaining a high index of suspicion for non-classical autoimmune manifestations.

CASE SERIES

Case 1: type 1 diabetes mellitus with autoimmune hepatitis

A 9-year-old boy, known case of T1DM, was diagnosed 4 months back when he had complaints of polyuria, polydipsia, weight loss and had presented in DKA. He was initiated on subcutaneous basal bolus insulin therapy and achieved satisfactory glycemic control. Four months later, he presented with progressive jaundice and abdominal distension for two weeks along with swelling of the feet since the last 7 days. On further enquiry, a similar episode of jaundice had occurred one month earlier which had resolved spontaneously without medical evaluation.

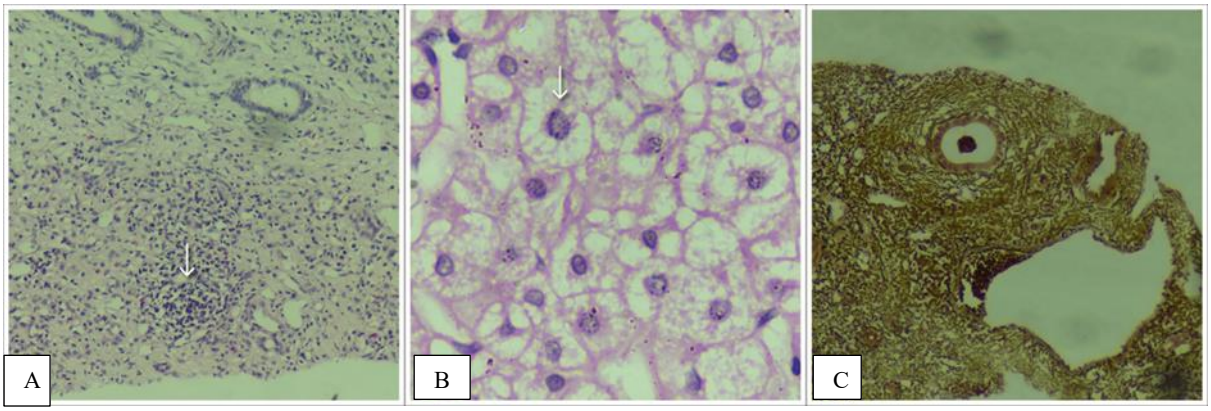

Figure 1: Liver biopsy image of patient 1 showing: (A) low power photomicrograph (H and E, 10x) of liver biopsy showing portal tract expansion by inflammatory infiltrate and interface hepatitis (arrow), (B) high power photomicrograph (H and E, 40x) showing lobular inflammatory activity with hepatocyte ballooning degeneration (arrow) and (C) special staining (reticulin stain, 10x) showing preserved hepatic architecture.

No history of any drug intake. Perinatal history was uneventful with normal development and immunisation upto age. The child was born of a non-consanguineous marriage with no family history suggestive of autoimmunity. Anthropometric parameters were normal and examination showed icterus and bilateral pitting pedal edema. Abdominal examination revealed ascites, liver span of 7.5 cm and spleen palpable 8 cm below the left costal margin.

In view of the waxing and waning course of liver disease in a child with T1DM, autoimmune hepatitis was considered as the primary differential, with viral hepatitis and metabolic liver disease being other possibilities. Investigations revealed conjugated hyperbilirubinemia (total bilirubin 3.24 mg/dl; direct fraction 2.21 mg/dl), mildly elevated transaminases (ALT 64 u/l, AST 87 u/l), hypoalbuminemia (1.94 g/dl) with albumin–globulin reversal and an INR of 1.3. Alkaline phosphatase and gamma-glutamyl transpeptidase levels were normal. There was no evidence of hemolysis with haemoglobin being 9.2 g/dl, normal lactate dehydrogenase levels and no features of hemolysis on peripheral blood smear. HbA1c was 7%, ruling out jaundice due to Mauriac syndrome as a result of uncontrolled hyperglycemia in T1DM.

Serology for Hepatitis A, B, C and E was negative. Wilson's disease was ruled out by normal serum ceruloplasmin levels and urine copper studies. Antinuclear antibody, anti–liver–kidney microsomal-1 and anti-mitochondrial antibodies were positive with negative anti-smooth muscle antibody, suggestive of type 2 autoimmune hepatitis as per the Simplified Autoimmune Hepatitis (AIH) scoring system.[7] Ultrasonography of the abdomen showed coarse hepatic echotexture with splenomegaly and mild to moderate ascites. Liver biopsy demonstrated dense portal inflammatory infiltrates, interface hepatitis, hepatocyte ballooning, emperipolesis and hepatocyte rosette formation, consistent with the diagnosis of autoimmune hepatitis (Figure 1). The child was started on oral

corticosteroid therapy. To maintain optimal glycaemic control, the insulin dose was titrated and escalated up to 1.8 U/kg/day. Screening for other autoimmune conditions, including autoimmune thyroid disease, celiac disease and adrenal insufficiency, was negative. The liver disease showed a good response to corticosteroid therapy with clinical improvement and a gradual reduction in serum bilirubin and transaminase levels on follow-up.

Case 2: immune thrombocytopenic purpura preceding type 1 diabetes mellitus

A 7-year-old girl presented with a history of increased thirst, frequent urination and weight loss since last one month. Perinatal history was uneventful with normal development and no significant family history. Her past medical history was significant as at 3 years of age, she had presented with acute onset bleeding manifestations in the form of petechiae, bleeding from gums and blood in urine and stools (Figure 2). She did not have organomegaly or lymphadenopathy. Complete blood count revealed isolated thrombocytopenia (platelet count 2,000/µl) and peripheral smear showed reduced platelets with normal morphology. She was diagnosed with ITP. Bone marrow examination revealed trilineage haematopoiesis with megakaryocytic hyperplasia, consistent with ITP.

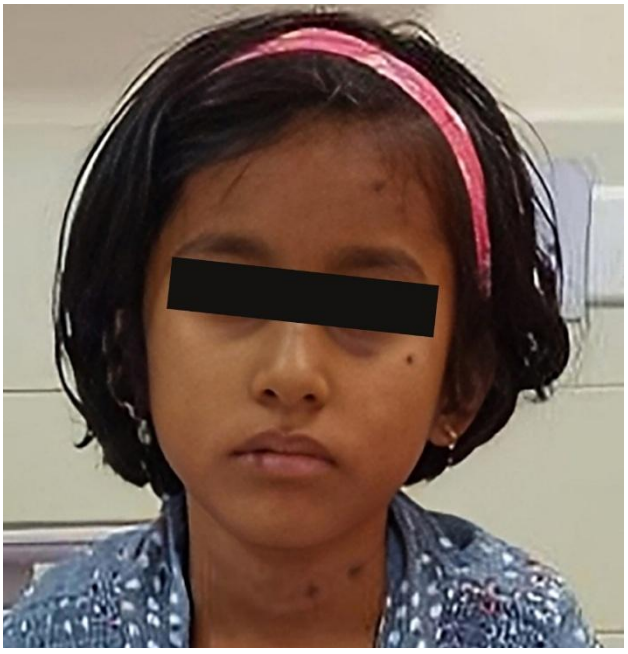

Figure 2: Clinical photograph of patient 2 showing petechial lesions over the face and neck consistent with cutaneous bleeding manifestations of immune thrombocytopenic purpura.

Over the subsequent four years, she had a relapsing course with four hospital admissions for bleeding manifestations, each requiring intensive treatment with systemic corticosteroids and intravenous immunoglobulin (IVIG). In view of frequent relapses and a chronic refractory course of ITP, she was started on oral thrombopoietin receptor agonist Eltrombopag, following which her platelet counts stabilized.

At seven years of age, four years after the initial diagnosis of ITP, she presented with polyuria and polydipsia of two weeks' duration. On evaluation, she was found to have hyperglycaemia (RBS-525 mg/dl), ketonuria (urine ketones 4+), blood gas showing metabolic acidosis (pH 7.2, HCO3 16 mmol/l) and was diagnosed with type 1 diabetes mellitus, presenting as mild diabetic ketoacidosis (DKA). The presence of ketoacidosis with ketonuria along with markedly elevated HbA1c (>14%) and low C-peptide levels, established the diagnosis as type 1 diabetes mellitus rather than steroid-induced hyperglycaemia. She was managed with standard DKA protocol, achieved metabolic stabilization and was transitioned to subcutaneous basal–bolus insulin regimen.

She subsequently experienced two more relapses of ITP requiring hospitalization and pulse methylprednisolone therapy which significantly derailed her glycaemic control. She was initiated on steroid sparing agent Mycophenolate Mofetil (MMF) for refractory disease on which she did not have any further relapses. Screening for other autoimmune conditions, including autoimmune thyroid disease and celiac disease, was negative.

Case 3: type 1 diabetes mellitus with autoimmune hypoparathyroidism

An 8-year-old girl presented with polyuria, polydipsia and polyphagia for 20 days. Perinatal history was uneventful with normal development and immunisation up to age. The child was born of a non-consanguineous marriage with no family history suggestive of autoimmunity.

Anthropometric parameters and systemic examination were normal. Evaluation revealed random blood glucose of 550 mg/dl, urine ketones 3+ and metabolic acidosis. Liver and renal function tests with electrolytes, including serum calcium, were normal. HbA1c was markedly elevated (12%), C-peptide levels were low and she was diagnosed with T1DM, managed as DKA and discharged on subcutaneous insulin therapy.

Two years later, she presented with complaints of episodic involuntary muscle contractions with tightening and occasional tingling and sensation of numbness over lower limbs since the last 15 days. Examination revealed a positive Trousseau's sign, suggestive of latent tetany with systemic examination being unremarkable (Figure 3). Investigations showed hypocalcemia (total calcium 6.5 mg/dl, ionized calcium 0.9 mmol/l), hyperphosphatemia (14.7 mg/dl) with normal magnesium and renal functions. Vitamin D levels were mildly insufficient (25-hydroxy vitamin D 23 ng/ml) with inappropriately low intact parathyroid hormone (8.99 pg/ml). In view of hypocalcemia with hyperphosphatemia

and low parathyroid hormone in a child with T1DM, a diagnosis of autoimmune hypoparathyroidism was made. She was started on oral calcium (40 mg/kg/day) and calcitriol (0.75 µg/day) on which she attained normocalcemia. Autoimmune thyroid disease, celiac disease and adrenal insufficiency screen was negative.

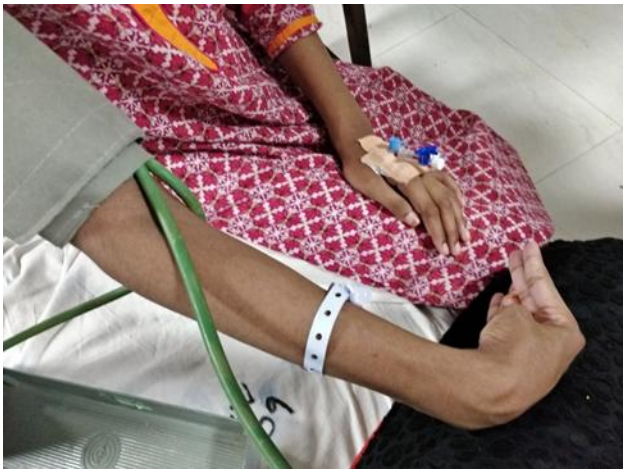

Figure 3: Clinical photograph showing positive Trousseau's sign in patient 3, indicative of latent tetany due to hypocalcaemia in autoimmune hypoparathyroidism.

At 12 years of age, after two years of follow-up, her calcium profile is normal on therapy. She has had three episodes of DKA, precipitated by vaginal candidiasis with KOH mount suggestive of budding yeast cells and lipohypertrophy being possible incriminating factors. Her current insulin requirement is 1.7 U/kg/day. In view of T1DM, autoimmune hypoparathyroidism and recurrent candidiasis, she is suspected to have autoimmune polyglandular syndrome type 1–like phenotype for which genetic evaluation for Autoimmune regulatory (AIRE) gene mutation is planned. She is under annual surveillance for adrenal insufficiency.

DISCUSSION

The coexistence of T1DM with other autoimmune diseases is well recognized and reflects a shared background of immune dysregulation. While autoimmune thyroid disease and celiac disease account for the majority of associated conditions in children with T1DM, growing evidence suggests that immune involvement may extend beyond classical endocrine organs.[1,2] The present case series illustrates three distinct and uncommon autoimmune manifestations involving the liver, hematologic system and parathyroid glands, emphasizing the heterogeneous nature of autoimmune clustering in paediatric T1DM. Several longitudinal studies have demonstrated that additional autoimmune diseases in T1DM often develop sequentially rather than concurrently, sometimes years after the diagnosis of diabetes.[2-8] This pattern was evident in all three of our patients, supporting the concept of progressive loss of immune tolerance. Genetic predisposition, shared HLA haplotypes and abnormalities in immune regulatory pathways are believed to play a central role in this phenomenon.[3-9]

Autoimmune hepatitis (AIH) is an uncommon but recognized autoimmune association in children with T1DM. Hovinga et al reported a child with T1DM who developed autoimmune hepatitis confirmed on liver biopsy, highlighting the diagnostic challenge posed by fluctuating liver enzymes and delayed presentation.[4] Similarly, Al-Hussaini et al demonstrated the presence of autoimmune hepatitis–related autoantibodies in children with T1DM, suggesting a shared autoimmune basis between the two conditions.[10] The first case in our series reinforces these observations and emphasizes the importance of considering AIH in children with T1DM presenting with recurrent jaundice, hepatosplenomegaly or features of chronic liver disease. Notably, AIH may present with only mild transaminase elevation despite significant histopathological involvement, underscoring the need for early liver biopsy when clinical suspicion is high. In such children, corticosteroids remain the mainstay of therapy; however, their use is a double-edged sword as it has a significant adverse impact on glycaemic control.

Immune thrombocytopenic purpura represents another rare non-endocrine autoimmune association with T1DM in children. Tschudin et al reported two paediatric cases having an unusual association of T1DM with ITP not conforming to a diagnosis of typical autoimmune polyglandular disease.[5] Quintana et al further reported improvement in glycaemic control following treatment of ITP, supporting a shared immune-mediated pathogenesis.[6] In our second case, ITP preceded the onset of diabetes by several years and followed a chronic relapsing course, ultimately necessitating treatment with a thrombopoietin receptor agonist. The need for corticosteroid therapy during ITP relapses poses a therapeutic challenge due to steroid-induced hyperglycaemia, further compounding glycaemic instability in children with T1DM, presenting a significant management dilemma.

Autoimmune polyglandular syndrome type 1 (APS-1) is an autosomal recessive disorder caused by mutations in the AIRE gene which is classically characterised by the triad of hypoparathyroidism, adrenal insufficiency and chronic mucocutaneous candidiasis.[11] Subsequent reports have also documented the coexistence of T1DM within the APS-1 spectrum.[12,13] Perheentupa et al in a Finnish series of 89 APS-1 patients described T1DM in 18%.[11] The third case in our series, characterized by autoimmune hypoparathyroidism, recurrent mucocutaneous candidiasis and T1DM is suggestive of an evolving APS-1–like phenotype. The absence of adrenal insufficiency at present highlights the progressive nature of autoimmune disease in such patients and underscores the importance of long-term surveillance. Collectively, these cases

demonstrate that autoimmune involvement in paediatric T1DM can extend beyond classical endocrine associations and may involve diverse organ systems. Restricting evaluation to routine screening alone may result in delayed diagnosis and increased morbidity. Awareness of such non-classical autoimmune manifestations and a low threshold for targeted evaluation are essential for early diagnosis, appropriate management and improved long-term outcomes in children with T1DM.

CONCLUSION

This case series highlights the expanding and heterogeneous spectrum of autoimmune disorders that may occur in children with T1DM beyond the commonly recognized associations. Autoimmune hepatitis, immune thrombocytopenic purpura and autoimmune hypoparathyroidism, though uncommon, represent clinically significant manifestations of immune dysregulation in paediatric T1DM. This should be kept in mind during the long term follow up care of T1DM children so that any such suggestive clinical symptoms can be picked up and evaluated at the earliest. Identification and self-reporting of such symptoms pertaining to other possibly involved organ systems should also be incorporated in Diabetes health education given to these children and their caregivers.

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