Atypical ketosis-prone diabetes

S. Ali Imran MB BS FRCP FRCPC Ehud Ur MB BS FRCP

Atypical diabetes is a rare form of diabetes mellitus (DM) that presents with diabetic ketoacidosis (DKA). However, in contrast to type 1 DM, patients with atypical DM undergo spontaneous remission and maintain long-term insulin independence. Family physicians must maintain a high index of suspicion to diagnose and manage such cases.

Case description

A 44-year-old, previously healthy South Asian woman presented to her family physician with progressively worsening dry mouth, polyuria, and polydipsia for 6 weeks. She had also lost 7 kg in weight over the past 3 months. At the time of initial presentation, her fasting glucose was 18.1 mmol/L and her hemoglobin A_{1c} was 13.4% (normal 4.5% to 6.5%). Results of the urinalysis were positive for glucose (>55 mmol/L) and ketones (>7.8 mmol/L). The family physician made a clinical diagnosis of type 1 DM and referred her to the local diabetes management centre. She was seen the same day at the diabetes centre and started on intensive insulin therapy, with multiple daily injections, after consultation with the endocrinologist.

Upon presentation her weight was 63 kg with a calculated body mass index of 23.4 kg/m^2. She had no family history of DM, and test results were negative for anti-islet cell and anti–glutamic acid decarboxylase (anti-GAD) antibodies. Within a few weeks of starting insulin therapy, her insulin requirement gradually started coming down; after 2 months she was able to discontinue insulin completely. At that stage, her fasting insulin and C-peptide levels were both normal at 36 pmol/L (normal 14 to 145 pmol/L) and 695 pmol/L (normal 364 to 1655 pmol/L), respectively. Two years later she remained insulin independent and her diabetes remained well controlled without any pharmacologic intervention. Her premeal glucose readings consistently ranged between 5 and 7 mmol/L, and her hemoglobin A_{1c} was 6.1%.

Discussion

For the preparation of this article, MEDLINE was searched from January 1966 to May 2008 using the key words *atypical diabetes, flatbush diabetes,* and *ketosis-prone type 2 diabetes*. Atypical or ketosis-prone type 2 DM was originally described by Winter et al[1] among African-American patients who presented with DKA as the initial manifestation of DM but whose subsequent course resembled that of type 2 DM. Since then, however, it has been reported in other ethnicities, such as Chinese[2] and Japanese.[3] The mean age of presentation is 40 years, with 2- to 3-fold higher preponderance in men.[4,5] The prevalence of obesity is high among these patients and more than 80% have a family history of type 2 DM.[6] Typically, these patients present with unprovoked DKA in association with a history of polyuria, polydipsia, and weight loss for less than 6 weeks. Although most patients undergo spontaneous remission requiring discontinuation of insulin therapy within a few weeks,[4,7] an estimated 60% to 70% of patients relapse within 2 years[7] and require either oral hypoglycemic agents or insulin.

Unlike type 1 DM, patients with atypical DM are characterized by the absence of markers of autoimmune β-cell failure, including antibodies against islet cells, insulin, and GAD. This lack of immunologic markers differentiates atypical DM from the slowly progressing type 1 DM. Although most patients with atypical DM have a family history of type 2 DM, the genetic susceptibility of atypical DM is not fully understood. While some investigators have reported a linkage with human leukocyte antigens DR3 and DR4,[8] others have failed to find such an association.[7] The emerging data do suggest a genetic susceptibility to atypical DM, but it is unclear if it is polygenic or associated with single gene defect.

The underlying pathogenesis of atypical DM is also unclear. Metabolic studies measuring β-cell function have consistently shown transient secretory defect of β cells during the acute phase, with 60% to 80% improvement in insulin-secreting capacity during remission.[7] This is coupled with a concomitant severe reduction in insulin sensitivity during the acute hyperglycemia phase, which is improved by 200% upon restoration of normoglycemia.[7,9] It has been suggested that the acute impairment of β-cell function might be partly due to glucose toxicity,[7] a phenomenon in which chronic hyperglycemia induces β-cell failure and insulinopenia, which improves with diabetes therapy.[10]

Management of atypical DM during the acute phase is similar to that of acute DKA and includes intensive monitoring and administration of insulin along with fluid and electrolyte replacement. A rapidly reducing insulin requirement over the next few weeks should alert the physician about the possibility of atypical DM. Immunologic markers of type 1 DM (ie, antibodies

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against insulin, islet cells, and GAD) should be checked; their absence strongly favours atypical DM. Normal fasting serum insulin and C-peptide levels after the discontinuation of insulin and achieving the state of normoglycemia further support adequate β-cell activity. Although some investigators recommend measuring C-peptide levels after intravenous glucagon stimulation to assess β-cell secretory function,[1,7] such testing is only feasible in specialized centres and is not necessary to make a diagnosis. After restoration of normoglycemia, these patients require close follow-up and should be advised to monitor their glucose levels on a regular basis. The long-term outcome for these patients is variable, but most patients develop hyperglycemia within 2 years of follow-up, requiring either oral hypoglycemic agents or low-dose insulin.[6,7] However, some patients do remain normoglycemic indefinitely.

Family physicians need to be aware of this unusual form of DM and be able to differentiate it from either slowly progressive type 1 DM or the "honeymoon phase" of type 1 DM. The slowly progressive form of type 1 DM, also known as latent autoimmune diabetes in adults or adult-onset type 1 DM, has a similar presentation to type 2 DM; however, individuals with this form typically have a lower body mass index and are less likely to respond to diet changes and oral hypoglycemic agents. The "honeymoon phase" of type 1 DM, on the other hand, is characterized by a period of decreasing insulin requirement a few weeks after the initial diagnosis and initiation of insulin therapy. This phase can last several weeks to months. However, both of these conditions are characterized by positive immunologic markers for type 1 DM. An absence of these markers would suggest atypical DM. Atypical DM should also be differentiated from acute hyperglycemia in type 2 DM, which typically does not present with acute weight loss, polyuria, polydipsia, hyperglycemia, and profound ketosis. Moreover, unlike type 2 DM, patients with atypical DM achieve spontaneous normoglycemia without further weight loss.

Conclusion

Atypical or ketosis-prone type 2 DM is a recently identified form of DM. It has been described in various ethnicities, and family physicians in an ethnically diverse country such as Canada are likely to encounter patients with this condition. The natural course of atypical DM is distinct from either type 1 or type 2 DM, and an awareness of this entity can facilitate early diagnosis and adequate management.

Dr Imran is an Associate Professor and **Dr Ur** is a Professor in the Division of Endocrinology and Metabolism at Dalhousie University in Halifax, NS.

Competing interests
None declared

Correspondence
Dr S.A. Imran, Division of Endocrinology and Metabolism, Dalhousie University, 7th Floor, North Victoria Building, VG Site, 1278 Tower Rd, Halifax, NS B3H 2Y9; telephone 902 473-8277; fax 902 473-3726; e-mail **ali.imran@cdha.nshealth.ca**

EDITOR'S KEY POINTS

- Most of us have been taught that all patients who present with diabetic ketoacidosis will require lifelong insulin; however, this is not always the case.
- Atypical diabetes is a rare form of diabetes, in which patients presenting with diabetic ketoacidosis will have spontaneous resolution of their diabetes within a few weeks. Most patients will relapse within 2 years of diagnosis, requiring insulin or oral hypoglycemic agents.
- Early management of atypical diabetes is similar to that of type 1 diabetes mellitus; however, a rapidly falling requirement for insulin over the first few weeks should alert physicians to the possibility of this diagnosis. Patients with atypical diabetes typically have negative markers of autoimmune β-cell failure.

POINTS DE REPÈRE DU RÉDACTEUR

- On a enseigné à la plupart d'entre nous que les patients qui présentent une acidocétose diabétique auront besoin d'insuline pendant toute leur vie; pourant ce n'est pas toujours le cas.
- Le diabète atypique est une forme rare de diabète dans laquelle les patients qui présentent une acidocétose verront une disparition spontanée de leur diabète en quelques semaines. La plupart des patients feront une rechute au cours des 2 années suivant le diagnostic et auront besoin d'insuline ou d'agents hypoglycémiques par voie orale.
- La prise en charge initiale du diabète atypique est semblable à celle du diabète de type 1; cependant, un besoin d'insuline qui décroît rapidement au cours des quelques premières semaines devrait alerter les médecins de cette possibilité. Les patients atteints de diabète atypique ont habituellement des marqueurs négatifs d'insuffisance auto-immune de cellules.

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