Diagnostic Dilemma: Clinical and Histological Abnormalities in a Hispanic Patient With Diabetes

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CASE SUMMARY

- Hispanic male died at age 34 years
- Diabetes duration 21 years (diagnosed at age 13 years with type 1 diabetes)
- BMI 23.5 kg/m^2
- HLA A*02:06,24:02; DRB1*04:07,14:06; DQA1*03:01,05:01; DQB1*03:01,03:02 not associated with either risk or protection for type 1 diabetes
- Type 1 diabetes–associated autoantibodies negative at time of death; HbA_{1c} not available
- High C-peptide (3.18 ng/mL) at time of death despite 21-year history of presumed type 1 diabetes (nonfasting C-peptide $<$0.6 ng/mL suggests absolute insulin deficiency [1])
- Medical comorbidities included hypertension and end-stage renal disease on hemodialysis for 1.5 years prior to death
- Social history of occasional alcohol consumption (wine 1/month, liquor 3/month) and cigarette smoking (2 pack-years)
- Became unresponsive at home, developed respiratory insufficiency, was intubated, and suffered an intracranial hemorrhage that progressed to brain swelling and death 12 days later
- Cause of death: stroke

CASE NARRATIVE

The review of organ donors' medical history is often limited to the terminal hospitalization records. This 32-year-old Hispanic patient had a history of type 1 diabetes since age 13 years and was treated with insulin since diagnosis. However, we have reasons to challenge the clinical diagnosis. The HLA region provides the highest contribution to genetic risk for type 1 diabetes (2). Although the HLA profile observed for this patient is not known to be associated with either risk or protection (2,3), there has been a recent rise in type 1 diabetes incidence among patients with HLA considered to confer lower risk for developing the disease (4). The absence of type 1 diabetes–associated autoantibodies (i.e., glutamic acid decarboxylase, insulinoma-associated protein 2, zinc transporter 8) at the time of study may be attributable to autoantibody loss over time; the absence altogether has been reported in type 1 diabetes in a mere 10% of cases at diagnosis (5). Although only 5%–10% of all diabetes is type 1, the vast majority of patients are diagnosed when they are children and young adults. Although there is increasing awareness of latent autoimmune diabetes in adults, it is most often diagnosed as type 2 diabetes (6).

The Network for Pancreatic Organ Donors with Diabetes (nPOD) collects pancreas and other tissues relevant to type 1 diabetes pathogenesis from organ donors. Through this initiative, we have been able to confirm at and near the time of type 1 diabetes diagnosis the characteristic pathology of insulitis defined as the presence of $\geq$6 $CD3^+$ cells adjacent to or within an islet in $\geq$3 islets per section (7). These findings are most often associated with the loss of insulin-positive β-cells (pseudoatrophic islets) and reduction in islet number and size (7). In this donor (nPOD case 6263), histological findings include insulin-positive islets of normal size and numbers, along with severe, multifocal amyloidosis, a characteristic seen most often in patients with clinically diagnosed type 2 diabetes (Fig. 1). Although the presence

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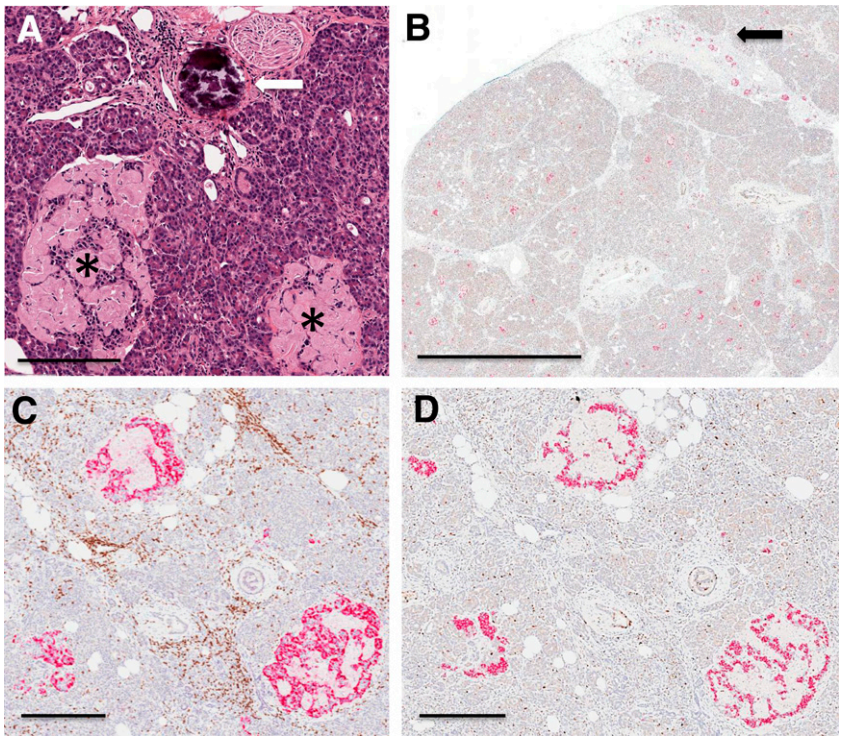

Figure 1—Representative islet images from nPOD case 6263. Serial paraffin sections were stained by hematoxylin-eosin (*A*) or double immunohistochemistry for Ki67+insulin (*B* and *D*) or CD3+glucagon (*C*), as previously described (4). *A*: Severe islet amyloidosis (*) was observed with calcification (white arrow) within atherosclerotic arteries seen in most pancreatic regions. *B*: A cross-section of the pancreas body shows high numbers of insulin-positive islets, including those within fibrotic regions (black arrow), with severe acinar cell loss. Severe amyloidosis is also seen in two islets with infiltration of the surrounding exocrine region by $CD3^+$ cells and fat cells (*C*). β-Cells (*D*) are present in each islet. Scale bars: *A*, 200 μm; *B*, 5 mm; *C* and *D*, 400 μm.

of insulin-containing β-cells is consistent with observed C-peptide production, the finding is unexpected in type 1 diabetes where significant reductions in β-cell mass are a defining feature of the disease (7). Should these histological findings necessarily change the diagnosis, or is there more to the story of histology and etiology potentially affected by factors such as race, ethnicity, sex, or age? Clinical features of type 2 diabetes include obesity, physical features of insulin resistance, and a family history of type 2 diabetes, whereas the most significant factors strongly correlating with type 1 diabetes have been age at diagnosis <35 years and time to insulin of <6 months (8). This donor was diagnosed and treated as having type 1 diabetes since childhood, with no presumed features of type 2 diabetes, yet presents contradictory histological features along with high C-peptide levels and no type 1 diabetes–related autoantibodies.

A monogenic diabetes genetic panel evaluating common and rare forms of maturity-onset diabetes of the young was performed and demonstrated a heterozygous mutation of AKT2 exon 5 of unknown significance. AKT2 plays a role in insulin action through insulin receptor kinase–mediated signaling (9). Activating mutations in AKT2 have been associated with hypoinsulinemic hypoglycemia (10), and loss of AKT2 function results in severe insulin resistance (11,12). Thus, it is possible that this donor possessed a completely unique form of diabetes, not as yet characterized; alternatively, this may be one of many examples of heterogeneity in type 1 diabetes pathogenesis (13). Further studies are required to determine whether this AKT2 polymorphism may have contributed to the dichotomous clinical and histological picture—information that will be critical as we move into individualized and precision medicine.

The clinical information available was not sufficient to initially refute the diagnosis of type 1 diabetes. Whereas type 1 diabetes affects mostly non-Hispanic white people in the U.S., there is still marked heterogeneity among those affected. The SEARCH for Diabetes in Youth (SEARCH) study demonstrated the incidence of type 1 diabetes among 10- to 14-year-old non-Hispanic white youth to be 32.9/100,000 compared with 17.6/100,000 for Hispanic youth (14). Hispanic youth obesity rates in type 1 diabetes were greater than in non-Hispanic white youth and were similar to rates in African American youth (44%) (15). Type 2 diabetes in youth from 10 to 19 years old is more common in the Hispanic group than the non-Hispanic white group; however, the Hispanic group still falls behind the African American, Asian/Pacific Islander, and American Indian groups for incidence of type 2 diabetes in youth (14). Even within this population there is diversity based on geographic location in addition to independent and unique cultural practices and genetic variations (16). Type 2 diabetes is rising, but type 1 diabetes remains more prevalent in youth, even among Hispanic adolescents (16). More importantly, we know that minority youth have poorer diabetes control and are more at risk for deleterious consequences (17).

In sum, although diagnosed with type 1 diabetes, postmortem analysis in this donor revealed histological findings consistent with type 2 diabetes, elevated C-peptide levels suggesting possible type 2 diabetes or maturity-onset diabetes of the young, and a genetic polymorphism in AKT2. Together these findings suggest that an alternative diagnosis may be appropriate. How we move forward with unique cases of conflict between clinical diagnosis and histopathological findings is critical; genetic sequencing may provide the answer, but there is still much we do not know. Each new case adds more information to the growing understanding of all forms of diabetes. There are limitations to data obtained from a single organ donor, but studies of these unusual cases also offer a cornucopia of information, which will hopefully open the door for more effective clinical intervention in the coming age of personalized medicine.

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can be obtained through the JDRF nPOD website (www.jdrfnpod.org). This study used data from the Organ Procurement and Transplantation Network. Donor data sets are available through nPOD DataShare, an online database for collaborative communication organized around the nPOD specimen repository.

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