Clinicopathological Conference

Decompen.sated Diabetes
New Features of an Old Problem

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Case Presentation

Denzil D'Souza, MD

The patient, a 48-year-old black man, was first admitted to the hospital in late February 1993 because of fatigue, polyuria, polydipsia, and nocturia. To lose weight, he had been on a liquid diet and vitamins since November 1992 and had lost about 4.5 kg. He had remained active, working as an automobile mechanic. For several weeks before admission, he had been tired and weak and had noticed polyuria. On the day of admission he collapsed. The patient had not had a recent infectious illness. A brother and an aunt have diabetes mellitus; both take insulin.

On admission to the emergency department, the patient had a heart rate of 140 beats per minute, and his blood pressure was 81/53 mm Hg. Physical examination showed the patient to be obese (weight, 106 kg; height, 173 cm; body mass index, 35.5 kg/m²). Ears, nose, and throat were clear. There was a grade 2 mid-systolic murmur along the left sternal border. The lungs were clear to auscultation. The abdomen was soft, with positive bowel sounds. The liver edge was palpable at the right costal margin. Liver span by percussion was 9 cm. There was no lesion of the extremities. The serum Na⁺ was 140 mmol/L, K⁺ was 6.0 mmol/L, creatinine was 460 μmol/L, urea nitrogen was 30 mmol/L, glucose was 102.1 mmol/L, and osmolality was 342 mmol/kg. Anti-islet cell antibodies were negative. Analysis of arterial blood gases revealed a pH of 7.11, HCO₃⁻ of 11 mmol/L, PaCO₂ of 34 mm Hg, and base excess of −17 mmol/L. A test for ketones was positive in a 1/64 dilution of serum.

The patient was treated with intravenous fluids and infusion of insulin; his hyperglycemia promptly improved and the ketoacidosis resolved. At discharge in early March, he was advised to maintain a 2000-kcal/d diet for patients with diabetes and to take neutral protamine Hagedorn insulin twice daily.

Four days later, on the first follow-up visit, the patient reported numbness and tingling in the left leg and complained of shortness of breath. He said he had mostly remained in bed since going home. On examination, the patient had a temperature of 98°F, heart rate of 120 beats per minute, and blood pressure of 130/90 mm Hg. He was tachypneic, but the chest was clear to auscultation. His left leg was swollen, warm, red, and slightly tender. The left thigh was 5 cm greater in circumference than the right. The patient was readmitted to hospital with a clinical diagnosis of deep venous thrombosis. Anticoagulation with heparin was begun. A chest radiograph was negative. Ventilation-perfusion scanning of the lungs showed a high probability of pulmonary embolus.

On the third morning after admission, the patient became acutely dyspneic and diaphoretic. Examination showed that his heart rate was 150 beats per minute, blood pressure 93/57 mm Hg, and respiratory rate 32 breaths per minute. The chest was clear to auscultation. Cardiac P₂ was loud. Arterial blood gases on 100% O₂ by face mask were PaCO₂, 33 mm Hg and PaO₂, 48 mm Hg. Partial thromboplastin time was 32.9 seconds (normal, 25 to 35 seconds). A bolus of 5000 U heparin was given IV. He was taken immediately to the intensive care unit, where he received 100 mg tissue plasminogen activator (TPA) intravenously. About 10 minutes later, his dyspnea was improved, blood pressure had risen to 120/70, and oxygen saturation had increased from 85% to 98%.

The remainder of his hospital course was uneventful, except for development of partial occlusion of the left radial artery at the site of arterial punctures. Doppler imaging of the venous flow in the lower extremities showed thrombus in the left femoral and popliteal veins. After establishment of therapeutic anticoagulation with warfarin, he was discharged on March 22.

Since that time, he has gained about 11 kg. Despite the weight gain, his glycemia has gradually improved, and insulin was discontinued in June. In July, glyco-sylated hemoglobin was 4.3% (normal, 4.0 to 6.0). In September 1993, 1 hour after 100 g oral glucose, serum glucose was 13.6 mmol/L, and C-peptide was 940 pmol/L (normal, about 1200 to 2000 pmol/L).

Classification of Diabetes

Victor R. Lavis, MD

This case highlights current issues about the classification of diabetes mellitus. Table 1 summarizes some pertinent epidemiological, clinical, and pathophysiological characteristics of the most prevalent forms of diabetes in the United States.

Over about the last 15 years, through a series of epidemiological, immunological, and molecular investigations, "type 1" diabetes mellitus, or insulin-depen-
dent diabetes mellitus (IDDM), has been identified as an autoimmune disease (reviewed in Reference 1). Its characteristics include marked predilection for white persons and extreme geographic variability of prevalence. Although the incidence peaks during puberty, new cases occur throughout life, even into old age. Type I diabetes exhibits several features of autoimmune disease. First, there is marked dependence of susceptibility on HLA type, with the DR-3 and DR-4 antigens conferring greatest risk, at least among white populations. Second, early in the course of disease, sections of the pancreas show an inflammatory infiltrate of the islets. Third, in early stages of the disease, even before the onset of hyperglycemia, a high proportion of patients demonstrate circulating antibodies against islet-cell antigens, important among which are isofoms of glutamic acid decarboxylase (GAD). Finally, type I diabetes is associated with other immunologically mediated endocrine disorders, including idiopathic adrenal insufficiency, Graves' disease, and chronic lymphocytic thyroiditis. After some years of disease, patients typically become absolutely dependent on exogenous insulin for the prevention of metabolic decompensation; this situation is accompanied by complete beta-cell failure as manifested by undetectable levels of circulating C-peptide and absence of beta cells in microscopic sections of the pancreas.

In contrast, the most common form of diabetes, especially in the United States, differs from type I in several respects (reviewed in Reference 2). The hereditary component to predisposition is stronger than for type I diabetes. Prevalence increases progressively with age throughout life. This form of diabetes is not associated with HLA type, and it is not accompanied by any detectable immunological attack on the pancreas. There is a strong relation to obesity, and a hypocaloric diet can improve or eliminate hyperglycemia. The pathophysiology is dominated by impairment of the action of insulin ("insulin resistance"). Although insulin secretion, especially in response to hyperglycemia, is definitely subnormal, patients usually have detectable and often substantial circulating insulin levels. Even after many years of diabetes, patients do not require exogenous insulin to prevent metabolic decompensation. Ketoacidosis ordinarily occurs only in the context of a stressful event such as severe infection or infarction of an organ. In the United States, this is the most prevalent form of diabetes among whites of European descent. Its prevalence is greater still among Native Americans, Blacks, and Mexican-Americans.4 The use of the term "type II diabetes" to describe this syndrome is unfortunate, because it implies a grade of pathogenic uniformity for which there is no good evidence. There may well be several pathways to the development of non–type I diabetes; therefore, I prefer an entirely descriptive term such as non–insulin-dependent diabetes mellitus (NIDDM).

Over the past several years, it has become clear that there are patients whose clinical courses fit neither the picture of IDDM (type I diabetes) nor that of typical NIDDM. One set of patients, reported first by Irvine et al8 and later by Groop et al9 and Tuomi et al,7 consists of whites who, in middle age or later, develop the insidious onset of nonketotic hyperglycemia but then progress to insulin dependency over a relatively few years. These individuals display the HLA markers and anti-GAD antibodies typical of type I diabetes. They probably have type I diabetes, with hyperglycemia beginning at an early stage, when some beta cells remain.

Another group not easily classified was reported by Winter et al.4 The patients were black, 12 of the 16 were obese, their diabetes did not correlate with HLA type, and islet-cell antibodies were absent; all these features suggest typical NIDDM. The manifestations at onset, however, were those of insulin deficiency, including weight loss, ketonuria, and in two cases, unprovoked ketoacidosis. Beta-cell secretory capabilities, assessed by measurement of stimulated C-peptide levels, were intermediate between those of normal individuals and those of patients with type I diabetes.

The patient in this report closely resembles those recently described by Banerji and associates.9 Their patients were black Americans, some of whom developed unprovoked ketoacidosis at ages 27 to 59 years.
These individuals were obese, with marked resistance to the action of insulin, as determined by the euglycemic clamp method. Stimulated levels of C-peptide were much higher than those of type I diabetics but definitely less than those of equally obese patients with typical NIDDM. These patients had frequencies of HLA DR-3 and DR-4 antigens approximately double that of typical NIDDM patients but showed no circulating antibodies suggestive of immunological attack on the pancreatic beta cells. After the initial episodes of ketoacidosis, 12 of the 21 patients remained free of ketosis from 1 to 18 months after withdrawal of insulin therapy.

Over the past few years, we also have seen several obese patients similar to the one described here, with onset of diabetes after the age of 40 years, presenting with unprovoked ketoacidosis. After their metabolism was stabilized, the patients could be treated for months without exogenous insulin, although some are now taking insulin.

Important questions concerning the pathogenetic classification of diabetes mellitus remain to be answered. Probably there are many ways to acquire the combination of insulin resistance and impaired beta-cell function that leads to symptomatic hyperglycemia. Although there seems to be a common syndrome of hereditary ketosis-resistant diabetes that correlates strongly with age and obesity, there are also patients who have neither this syndrome nor type I diabetes. Consequently, it seems premature to apply the term "type II" to all individuals with non-type I diabetes. Patients such as ours present a number of opportunities for future research. Longitudinal studies should help determine whether beta-cell function in such patients will decline progressively over the years. While the presentation with ketoacidosis does imply a degree of beta-cell vulnerability greater than in ordinary NIDDM, we do not know whether the beta-cell insulin secretion is transitory or progressive or what the pathophysiological mediators of beta-cell impairment are in these cases. We will have to identify and characterize these mediators if we wish to develop measures to retard or prevent the onset of insulin dependence.

Another area for future research is the attempt to design therapeutic regimens on the basis of physiological profiling—for example, to determine whether measuring simple indexes of beta-cell function at onset will predict future response to sulfonylureas.

**Thromboembolism in Diabetes**

**Victor R. Lavis, MD**

This case serves as a reminder that patients with compensated diabetes probably are at increased risk for development of thromboembolic events. In several large series of adult patients with diabetic ketoacidosis or nonketotic hyperosmolar hyperglycemia,10-17 deaths from thromboembolism and disseminated intravascular coagulation accounted for 20% to 50% of the total mortality, as summarized in Table 2. From 3% to 30% of the deaths were related to venous thrombosis. These numbers, which do not take into account the nonfatal and undiagnosed events, clearly underestimate the risk of thromboembolic complications.

The factors that interact to promote intravascular thromboses in patients with uncomplicated diabetes may be considered in the context of Virchow's triad18 of stasis, hypercoagulability, and endothelial damage. In decompensated diabetes, immobility and severe depletion of intravascular volume contribute to stasis.

Human diabetes, especially during metabolic decompensation, appears to be a hypercoagulable state. As reviewed elsewhere19,20 hyperreactivity of platelets, ex vivo and in vivo, has been found in both clinical and experimental diabetes, although there have been contradictory reports.21 The platelet abnormalities may have greater roles in arterial thrombosis and atherogenesis than in development of venous thrombosis. Hyperfibrinogenemia has also been reported, especially in patients with NIDDM, as reviewed in Reference 22. In these patients, elevated fibrinogen levels may be more closely related to obesity or atherosclerosis than to diabetes per se. Other clinical investigations have shown evidence for diminished fibrinolysis (reviewed in References 20 and 23 through 25). Elevated plasma levels of plasminogen activator inhibitor 1 (PAI-1) have been described in patients with NIDDM but not those with type I diabetes (reviewed in Reference 24). Since PAI-1 levels correlate with degree of obesity as well as plasma levels of insulin and triglycerides,25 it appears that circulating PAI-1 is related primarily to insulin resistance rather than to the diabetic state per se. Circulating PAI-1 appears to be a marker for risk of arterial thrombosis; its role in venous thromboembolism is not yet known.

Elevation of circulating levels of von Willebrand factor has been reported especially in those diabetic patients with nephropathy or retinopathy,26-27 suggesting a relation to endothelial dysfunction. In one series, increased levels of von Willebrand factor were associated with decompensated diabetes.28 Some investigators29 have reported reductions of circulating von Willebrand factor levels concomitant with institution of improved glycemic control, implicating a direct role for metabolic dysfunction, but others have found no such relation.

In general, the thrombogenic abnormalities have been reported to be more prevalent and more severe in patients who have microvascular disease (retinopathy, albuminuria) or symptomatic atherosclerosis than in those who have uncomplicated hyperglycemia. Perhaps hypercoagulability predisposes to diabetic angiopathy. Alternatively, atherosclerosis, microangiopathy, nephrop-

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athy, and coagulopathy may all reflect a more fundamental underlying disorder of endothelial function.

Further investigations in this area will be aided by development of sensitive and reliable tests that will reflect the activities of platelets and the coagulation and fibrinolytic pathways in vivo.

**Thrombolytic Therapy for Pulmonary Thromboembolism**

Steven D. Brown, MD

Hemodynamic compromise after pulmonary thromboembolism is directly proportional to the reduction in the cross-sectional area of the pulmonary capillary bed by the embolus or the subsequent vasoconstriction. Although hypoxemia commonly occurs after pulmonary thromboembolism, acute morbidity and mortality are often related to acute pulmonary hypertension, subsequent right ventricular failure, and a fall in cardiac output.

Three thrombolytic agents have been investigated for their ability to reverse hemodynamic compromise after pulmonary thromboembolism; streptokinase, urokinase, and TPA. All three activate the inactive proenzyme plasminogen, which circulates either free in plasma or noncovalently bound to fibrinogen and fibrin, converting plasminogen to plasmin. Despite its name, streptokinase is not an enzyme. Streptokinase binds and activates plasminogen, and the resultant streptokinase-plasmin complex activates adjacent plasminogen but does not degrade fibrin. Antibodies against streptokinase, a bacterial protein, are common and may lead to allergic reactions or to rapid binding of streptokinase and decreased thrombolytic efficacy. Urokinase, a naturally occurring human protein, activates free and fibrin-bound plasminogen directly. Unlike streptokinase and urokinase, TPA, also a naturally occurring protein, is relatively more specific for the activation of fibrin-bound plasminogen. This property, however, has yet to translate into clinical advantage. Free urokinase and TPA have half-lives of a few minutes, because they are quickly bound to inhibitors. Ideally, plasmin should cleave only cross-linked fibrin. Unfortunately, plasmin also cleaves fibrinogen, and systemic degradation of the coagulation system with a risk of hemorrhage occurs at currently recommended doses of all thrombolytic agents.

An early report described the possible advantages of thrombolytic therapy over conventional heparinization in a canine model of acute pulmonary thromboembolism and in four human cases. Although the trial was uncontrolled, two patients who did not improve hemodynamically on heparin alone promptly improved after streptokinase. The report raised a number of issues that remain unresolved, including the identification of the appropriate patient, the optimal duration of infusion and laboratory evaluation of the thrombolytic agent, and the concern for hemorrhage after thrombolytic therapies.

The Urokinase Pulmonary Embolism Trial compared urokinase followed by heparin with heparin therapy alone. Urokinase infused over a period of 12 hours produced more rapid improvement in pulmonary angio-grams, perfusion scans, and right-sided hemodynamic measurements than heparin alone. Neither therapy resolved emboli completely. However, no difference was observed in mortality or the recurrence rate of pulmonary thromboembolism between the two groups at 2 weeks, whereas the incidence of hemorrhage was 45% in the urokinase group and 27% in the heparin-only group. Hemorrhage was associated closely with the invasive procedures of the study. Younger patients with preexisting cardiopulmonary disease and a larger, more acute embolic load appeared to receive a greater benefit from urokinase. The subsequent Urokinase-Streptokinase Embolism Trial compared a 12-hour infusion of urokinase to a 24-hour infusion of streptokinase or urokinase (all followed by heparin) in the therapy of pulmonary thromboembolism. Clot resolution was equal in both urokinase groups and greater in the 24-hour urokinase group than in the streptokinase group. The difference in clot resolution between the urokinase and streptokinase groups was most pronounced in patients with massive embolism. Nonfatal allergic reactions occurred in 3 of 58 patients treated with streptokinase and 1 of 113 patients treated with urokinase.

Many studies have compared TPA with other agents as therapy for pulmonary thromboembolism. Although a 2-hour infusion of 100 mg of TPA lysed clot more rapidly than a 12-hour infusion of urokinase after 2 hours of therapy, the same authors subsequently demonstrated that a larger initial bolus of urokinase lysed clot as effectively as TPA. Nonfatal allergic reactions occurred commonly after urokinase but not after TPA. Right ventricular dysfunction and perfusion scans improved more rapidly after TPA followed by heparin than with heparin alone in hemodynamically stable patients who had acute pulmonary thromboembolism. In that study, pulmonary thromboembolism recurred in 5 of 55 patients treated with heparin only and in 0 of 46 patients treated with TPA.

Smaller doses of TPA infused over a shorter period of time, followed by heparin, may limit the expense and complications of thrombolytic therapy for pulmonary thromboembolism. In an uncontrolled study of massive pulmonary thromboembolism in 54 patients, 1 mg/kg TPA infused over 10 minutes improved lung perfusion scans at 48 hours and at 10 days and improved hemodynamics in 11 of 15 patients with shock. In a study of 58 patients with acute pulmonary thromboembolism, 0.6 mg/kg TPA infused over 2 minutes produced a larger improvement in perfusion scans at 24 hours than did heparin alone. However, no difference in perfusion scans between the two groups was observed 7 days after the initiation of therapy, and no recurrent embolism was observed in either group during the study period. Minor bleeding occurred in several patients treated with TPA.

Collectively, the literature on thrombolytic therapy for pulmonary thromboembolism demonstrates a more rapid improvement in the hemodynamics and lung scans of patients after thrombolytic therapy than after treatment with heparin alone. Thrombolytic therapy may be of greater hemodynamic benefit to patients who have larger rather than smaller emboli.

Streptokinase and urokinase are associated more often with allergic reactions than TPA, but most are not severe, and urokinase and TPA are substantially more expensive than streptokinase. Urokinase and TPA may
be equally effective, and shorter, lower-dose regimens probably will supplant longer, higher-dose regimens.

The incidence of hemorrhagic complications from thrombolytic therapy has been reduced by refraining from its use in invasive studies. However, no study of thrombolytic therapy for pulmonary thromboembolism has yet demonstrated an improvement in long-term survival, morbidity, or functional status. Nevertheless, it seems reasonable to consider immediate thrombolytic therapy for patients who have hemodynamic compromise or marginal hemodynamic reserve as a result of pulmonary thromboembolism.

Final clinical diagnosis: (1) diabetes mellitus with ketoacidosis; (2) left lower extremity venous thrombosis; and (3) pulmonary embolism.

References


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