tis from clinical examination, echocardiogram, and ventriculography suggests that valvular endocarditis was not present before or at the time of admission for surgical treatment. For this reason and because the Gram's stain of the aneurysmal wall showed no organisms, it seems unlikely that aortic valve endocarditis was responsible for the aneurysm development.

Although angiography is still considered by some the gold standard for the diagnosis of an SVA, if coronary artery assessment is not required, this case and others suggest that TTE with or without a TEE with color flow mapping may be an adequate diagnostic test for planning the surgical procedure in both SVA and coronary artery aneurysm repair.28 The use of continuous-wave and color flow Doppler imaging enhances the specificity. If further delineation of the shunt is required, peripheral venous administration of agitated saline solution can reveal a negative jet in a right-sided receiving chamber. The transthoracic windows for optimal viewing are the basilar parasternal long and short axes.5 In a review of 62 patients, the accuracy of echocardiography and angiography to define the receiving chamber, the presence of aortic insufficiency, and subaortic stenosis shows that the sensitivity and specificity for each method is 100% relative to intraoperative inspection.2 The weakness of echocardiography is its poor sensitivity to detect SVA-associated pulmonic stenosis and ventricular septal defects (50% and 70%, respectively); however, the angiographic detection of SVA-associated ventricular septal defect was only 50%.7

This is the first case in modern literature of a patient with autosomal dominant polycystic kidney disease in whom a ruptured SVA developed. The SVA formation may be an additional feature of autosomal dominant polycystic kidney disease related to renal and hepatic cysts and cerebral and aortic aneurysms by the unifying cause of a flaved gene product. In this case, the windsock deformity produced by the ruptured aneurysm mimicked a coronary artery fistula.

REFERENCES

Diabetic Neuropathic Cachexia

ASLAM GODIL, MD
DIANE BERRIMAN, MD
Loma Linda, California
STEVE KNAPIK, DO
MICHAEL NORMAN, DO
FOUZIA GODIL, MD
Victorville, California
ANTHONY F. FIREK, MD
Loma Linda, California

DIABETIC NEUROPATHIC CACHEXIA is a rare syndrome first described in 1974 and seen predominantly in patients in their sixth or seventh decade with mild non-insulin-dependent diabetes mellitus (NIDDM). It is characterized by substantial involuntary weight loss, anorexia, depression, severe autonomic dysfunction, and peripheral neuropathy that develop over a short period of time. Generally other specific end-organ complications of diabetes mellitus, like retinopathy or nephropathy, are absent. The cause remains unclear, and there are no known precipitating factors. Because of its highly variable and profound clinical presentation, this syndrome is often confused with neuropathic carcinomatosis or an occult cancer. The overall prognosis is good, and symptoms generally resolve spontaneously over one to two years.

In this age of constrained resources, it is important that this clinical syndrome be recognized and considered in patients with diabetes mellitus. Since the original report, about 25 cases have been reported in the English-language literature, with only three cases in females.4,5 Herein we report a case of diabetic neuropathic cachexia and review the literature.

Report of a Case

The patient, a 57-year-old man, was initially admitted to the Jerry L. Pettis Veterans Affairs Medical Center (Loma Linda, California) in December 1992 with a diagnosis of the new onset of NIDDM. His chief symptom at that time was an accelerated unintentional weight loss of 18 kg (40 lb) over six months. The patient had numbness and severe burning over the soles of his feet, progressing proximally to involve his legs, anterior abdomen, and midthoracic area, developing rapidly over the same period. He also had polyuria, polydipsia, blurring of vision, general weakness, fatigue, decreased appetite, early satiety, constipation, impotence, and depression with insomnia. He had no history of dysphagia, odynophagia, diarrhea, nausea, vomiting, or stool incontinence. He had

no relevant history of alcohol and tobacco use.

On presentation, the patient’s blood pressure was 144/96 mm of mercury, supine, with a pulse rate of 89 beats per minute and 135/92 mm of mercury, standing, with a pulse rate of 93 beats per minute. He weighed 59 kg (131 lb) with a height of 178 cm (70 in). He was pale and appeared chronically ill and depressed, with a general loss of subcutaneous tissue. Muscle wasting was noted, more in the lower than the upper extremities. Vibration sensation, deep tendon reflexes, and muscle strength were decreased in the lower extremities. The results of the physical examination were otherwise unremarkable.

A random serum glucose level was 40.0 mmol per liter (721 mg per dl), and a complete blood count, urinalysis, and routine chemistry values were normal. The patient was admitted to the hospital, given intravenous fluids, and treatment with an oral hypoglycemic agent—glyburide, 5 mg a day—was started. His serum glucose levels remained adequately controlled, with a follow-up glycosylated hemoglobin level of 0.069 (6.9%).

In February 1993, the patient was readmitted because of syncope, continued weight loss (now weighing 56 kg (124 lb)], and progressive paresthesias, impotence, weakness, and fatigue that limited his walking to only a few steps. On examination he was markedly orthostatic, with a blood pressure of 124/82 mm of mercury, supine, with a pulse rate of 107 beats per minute and 62/44 mm of mercury, standing, with a pulse rate of 110 beats per minute. He appeared more cachectic and chronically ill, with pronounced flattening of his affect. There was no evidence of retinopathy. The extremities showed profound symmetrical and diffuse wasting, with associated bilateral weakness in both proximal and distal muscle groups, more pronounced in the lower than the upper extremities. Reflexes were symmetrically decreased in both upper and lower extremities with absent ankle jerks. Sensory examination showed dysesthesias in his feet, legs, and hands extending up to the midanterior chest, diminished proprioception and vibration sense, and numbness of the feet and hands to light touch and pinprick, suggesting involvement of both large and small fibers. The patient’s gait was unsteady due to muscle weakness and paresthesias, and he had to use a cane. He was given support stockings with partial improvement in orthostatics. In March 1993, the patient was seen in the outpatient clinic and had continued weight loss (now 54 kg (120 lb)). His serum glucose levels remained under good control (range, 5.4 to 8.9 mmol per liter [98 to 160 mg per dl] at home) with a glycosylated hemoglobin level of 0.07. A regimen of low-dose amitriptyline hydrochloride at bedtime was started for his paresthesias.

The patient underwent an extensive workup that included chest x-ray, thyroid-stimulating hormone, thyroxine, triiodothyronine, vitamin B12, and folate levels, a rapid plasma reagin test, creatine kinase level, serum cortisol level, thyroid scan, magnetic resonance imaging of the thoracic spine, ultrasonogram of the liver, gallbladder, and pancreas, quantitative stool fat, colonoscopy, and esophagogastroduodenoscopy with a small bowel biopsy, all of which were normal. Electromyography and nerve conduction studies showed reduced amplitude of motor and sensory nerve action potentials and mild slowing of nerve conduction velocities, consistent with axonal injury.

Since his discharge, he has been observed in the medical clinic for about three years. In June 1993, the patient weighed 56 kg (123 lb) (a 1.4-kg [3-lb] weight gain), and since then he has gained 16 kg (35 lb), no longer has postural hypotension, and his paresthesias are greatly improved. He is able to walk with minimal difficulty. His depression and impotence have resolved, and he is main-
tained on a regimen of glyburide, 5 mg per day, and amitriptyline, 25 mg per day at bedtime.

Discussion

The cause of diabetic neuropathic cachexia remains unclear. From reported cases, no precipitating factors such as exposure to toxins or chemicals have been identified.14 Nerve and muscle biopsies in these patients have shown neurogenic atrophy in the muscle1 and pronounced involvement of both large and small fibers with axonal degeneration, no inflammatory cells or amyloid deposits, and normal vasa nervorum.15 This suggests that the neuropathy of diabetic neuropathic cachexia is not a microvascular disease process as usually seen in classic diabetic neuropathy. This theoretically could explain the reversibility of this process, although strong evidence is lacking.

Electromyography and nerve conduction studies reveal a reduced amplitude of motor and sensory action potentials and a mild reduction in conduction velocities, indicating peripheral polyneuropathy from axonal degeneration. Weight loss is attributed to anorexia due to depression and pain.1 There have been four cases of diabetic neuropathic cachexia and weight loss caused by malabsorption4 due to exocrine pancreatic insufficiency, with normal endoscopic retrograde cholangiopancreatography, although a correlation of pancreatic insufficiency with this syndrome is lacking. Depression is attributed to neuropathic pain, and as neuropathy clears, depression and anorexia resolve simultaneously. Impotence is not a consistent feature of this syndrome. It is thought to be due to inanition, depression, and possibly neuropathy. Because potency returns in most patients, a psychogenic basis or inanition would be a more likely cause.1

Diabetic neuropathic cachexia is seen predominantly in men in their sixth or seventh decade with NIDDM, usually a mild form, often well controlled with diet or an oral hypoglycemic agent.1 The classic presenting features are weight loss, peripheral neuropathy, autonomic neuropathy, and emotional changes. Rare cases have been reported in patients who are young,7 have insulin-dependent diabetes mellitus,7 and are female.3,5 Usually NIDDM and diabetic neuropathic cachexia are diagnosed simultaneously. Occasionally patients may have NIDDM for several years before this syndrome develops.5,6,8

The hallmark of this syndrome is the extreme rarity of specific associated microangiopathic end-organ complications of diabetes, such as retinopathy or nephropathy, despite profound neurologic involvement. Notable weight loss of as much as 60% of the total body weight is a consistent feature in these patients. Weight loss occurs rapidly, usually over a period of three to six months, and it is generally not related to the control of the diabetes mellitus. Weight loss in classic diabetic neuropathy is not unusual,9 but it is rare to have a weight loss of this magnitude.

The neuropathy of diabetic neuropathic cachexia is distinct from various other diabetic neuropathies (summarized in Table 1). Usually it is severe, peripheral, bilaterally symmetrical,4 occurs in close association with the onset of diabetes mellitus, and involves both sensory and motor components. Sensory symptoms may be a pure sensory loss, paresthesias, aching, burning, or shooting pain, and dysesthesias, all usually worse at night.1 They usually begin distally in the lower extremities and rapidly ascend over weeks to months to more proximal levels, as compared with months to years in classic diabetic neuropathy,8 and may eventually involve the upper extremities, chest, and abdomen.9 Motor manifestations include general wasting with weakness.1 Patients appear emaciated with decreased muscle strength, more pronounced in the proximal lower extremities than in the upper extremities.1 There has been a case of diabetic neuropathic cachexia progressing to a flaccid paralysis of the lower extremities and bowel incontinence.5 Deep tendon reflexes are usually symmetrically decreased, often with an absence of ankle reflexes.3,5,6 Position and vibratory sense is also decreased or absent.1,5,6

The most interesting feature of neuropathy is a spontaneous resolution of severe pain and other neuropathic symptoms within two years.1,4 There are a few cases in which mild paresthesias may persist.5,7 The average duration of neuropathy ranges from 12 to 48 months. Autonomic neuropathy is much less common than peripheral neuropathy in these patients. The effects of autonomic dysfunction include impotence, orthostatic hypotension, and, rarely, constipation.1,4,7,8

A case of neurogenic bladder confirmed by cystometry has been reported that presented as an abdominal mass and obstructive renal failure,3 with the eventual return of normal bladder function after diabetic neuropathic cachexia resolved. There is no doubt that autonomic involvement in these patients is underestimated because of the focus on the manifested sensory neuropathic complaints. The neuropathy of diabetic neuropathic cachexia should be differentiated from diabetic amyotrophy,11 which is typically seen in patients with long-standing diabetes mellitus, characterized by substantial weight loss and the acute or subacute onset of moderate to pronounced asymmetric wasting and weakness of the pelvic femoral muscles. This weakness is accompanied by back, hip, and thigh pain with preserved sensation in the regions of pain. The site of lesion appears to involve either lumbosacral roots or plexus. The prognosis is fair to good with good functional recovery.

Depression is universally associated with this syndrome.14 Frequent crying episodes, insomnia, anxiety, and irritability are the characteristic features. The painful peripheral neuropathy may be the primary cause for depression, as all these patients had no history of depression, and their depression resolved with resolution of the neuropathy. Most are able to resume normal activities, including employment, without a noted recurrence of depression.

The presentation of diabetic neuropathic cachexia in middle-aged to elderly men as profound weight loss and severe neuropathic pain would direct a physician to evaluate for an occult malignant tumor. Carcinomatous neuropathy has a prevalence of 2% to 3%13 and is predominantly
associated with cancers of the lungs, pancreas, stomach, ovaries, breasts, and lymphoma and leukemias. These patients usually have mixed peripheral neuropathy, often associated with ataxia.

The workup for diabetic neuropathic cachexia should be individually based. It is a diagnosis of exclusion, and because the symptoms in this syndrome generally occur rapidly in middle-aged or elderly patients, suggesting malignancy, the workup should be systemic, which can be both extensive and resource-intensive. A progressive “negative” evaluation in a patient with such a dramatic presentation often leads to the use of more esoteric and expensive technologies. In this age of constrained resources, it is important that this clinical syndrome be recognized and considered in patients with diabetes mellitus.

Treatment is primarily supportive and symptomatic. With the release of the Diabetes Control and Complications Trial results, there is evidence that the tight control of glucose levels in insulin-dependent diabetes mellitus delays the onset and slows the progression of diabetic neuropathy and other end-organ complications. The role of intensive therapy in patients with NIDDM is not clear. In diabetic neuropathic cachexia, a condition where there is no evidence of microvascular end-organ damage and that often presents early in the course of diabetes mellitus, the role of aggressive therapy is not clear. There have been cases in which tight glucose control with oral hypoglycemic agents and sometimes insulin produced some lessening of the neuropathic symptoms. The only evidence in favor of this is that there is an intracellular accumulation of sorbitol and a depletion of myoinositol in hyperglycemic states that abate with control of serum glucose levels. Some patients with diabetes with classic peripheral neuropathy have benefited from continuous insulin infusion.

Antidepressants are of great help in the symptomatic management of the neuropathy and depression associated with this syndrome. A case of diabetic neuropathic cachexia was reported in which a regimen of fluphenazine dihydrochloride and amitriptyline hydrochloride decreased the neuropathic pain within 24 hours after therapy was initiated, and the pain continued to resolve subsequently. Our patient was given amitriptyline, but the improvement of neuropathy was gradual, more consistent with the natural course of the disease. The use of agents like phenytoin, carbamazepine, and clonazepam has inconsistently lessened symptoms in classic diabetic neuropathy. They are worth a therapeutic trial, although their specific role in resolving symptoms in this syndrome is uncertain. Good nutritional support with a high-protein and -carbohydrate diet may be of considerable help because anorexia is the main factor leading to weight loss.

Strong reassurance to patients, optimistic views about the course of the disease, and close follow-up are important in managing these patients. The prognosis is good. The most intriguing feature of diabetic neuropathic cachexia is the propensity of symptoms to spontaneously resolve over one to two years. With the resolution of pain and lifting of the depression, anorexia abates, leading to weight gain in most cases, often to the original weight. Furthermore, patients regain the ability to walk and regain continence and potency. In some patients, mild paresthesias persist. Most patients resume their normal lifestyle, with most maintaining good diabetes control with diet alone or with a low-dose oral hypoglycemic agent. Follow-up for longer than five years has shown no relapse of this symptom complex.

REFERENCES