Steroid-Responsive Hypercalcaemic Nephropathy in Diabetes mellitus Probably due to Occult Sarcoidosis

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Dear Sir,

Extrapulmonary sarcoidosis is a difficult diagnosis to secure, the entity becoming a veritable conundrum without an abnormal chest roentgenogram or diagnostic tissue. Overdiagnosis and underdiagnosis occur frequently [1]. The incidence of hypercalcaemia in sarcoidosis varies between 11 and 18% [2]. I present a case of diabetes mellitus (DM) with steroid-responsive hypercalcaemic nephropathy that defied definitive deliberation.

Case Report

A 70-year-old female Caucasian with noninsulin-dependent DM of 14 years' duration developed hypercalcaemia (up to 3.6 mmol/l) 4 years ago, having been initially managed at another hospital. Bence-Jones protein, bone marrow aspiration and trephine, and serial estimations of plasma protein and tumour markers, including CA 125 and parathyroid hormone (PTH)-related peptide, were negative. Thyroid function tests and vitamin D estimations were normal (25-OHD 11.8 ng/ml; 1,25(OH)₂D 53 pg/ml). PTH was persistently suppressed. Angiotensin-converting enzyme (ACE) was mildly elevated (96 U/l; normal 8-57). Chest X-rays were reported normal. Mammography, thyroid, and total body bone scintiscanning were negative. Kveim test was negative. Renal impairment, modest proteinuria, and histopathological tubular interstitial damage with nephrocalcinosis without any evidence of renal sarcoidosis were established. She was placed on increased fluid and salt intake,

bicarbonate supplementation, along with a low calcium and vitamin D diet.

She consulted the Dubai Police Medical Services in November 1992. An anamnestic review revealed a dry cough disturbing sleep since the onset of the illness, weight loss (12.7 kg), and fatigue. Physical examination was normal. Hypercalcaemia (3.1 mmol/l), elevated serum creatinine (239 µmol/l) and erythrocyte sedimentation rate (ESR) (63 mm/h Westergren), normal immunoglobulin assay and fasting sugar along with cutaneous anergy to tuberculin and radiological focal right paracardiac intrapulmonary calcification were detected. The overall picture suggested sarcoidosis, a diagnosis that had been considered but regarded unlikely by the renal unit of the other hospital. She revealed that a hydrocortisone suppression test had not been undertaken.

Sarcoidosis-related hypercalcaemia is exquisitely sensitive to glucocorticosteroid. A low-dose steroid trial could lower sarcoidosis-related hypercalcaemia and obviate the need for a full-dose challenge (oral hydrocortisone 120 mg/day) with its inimical metabolic implications for diabetics, including hospitalization. With her informed consent, at the end of 6 weeks of prednisolone (5 mg built up gradually to 12.5 mg/day) there was considerable improvement

in her cough, fatigue, ESR (38 mm), calcium (2.29 mmol/L) and creatinine (97 µmol/L) without deterioration in diabetic status. The decision to continue low-dose steroid therapy indefinitely was approved by her physicians in the other hospital. Poststeroid surveillance showed normalization of both PTH and ACE values.

Presently, more than 2 years later, she receives prednisolone 5 mg daily, maintains normal calcium and creatinine levels without cough or fatigue, has regained 4.5 kg weight, and has resumed a normal calcium diet.

Discussion

Pauker and Kopelman [3] discuss the absence of a diagnostic gold standard in a case with prebiopsy probability of > 99%. This case, with a much lower clinical probability, is truly representative of occult sarcoidosis. Four years after the onset of the illness no tissue has become available to buttress the diagnosis, maintenance steroid therapy practically eliminates this possibility. Approximately one-third of sarcoidosis subjects maintain normal ACE levels. Besides, ACE levels are elevated in DM (with retinopathy) and other diseases [4]. PTH suppression does not distinguish between various causes of steroid-responsive hypercalcaemia, including vitamin D intoxication, sarcoidosis, or skeletal metastases. The diagnosis of sarcoidosis is one of exclusion and probabilistic inference and can involve an exercise of logic [1, 3]. Presentation with complaints directly related to disordered calcium homeostasis [2] and absence of gastrointestinal features are unusual features in this case. Occult malignancy seems unlikely on the basis of chronicity. Fatigue, weight loss, and nonproductive cough occur in up to 60, 28, and 30% of sarcoidosis subjects, respectively [5].

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steroid decline of ACE is specific for sarcoidosis [4] and particularly remarkable in diabetic subjects. Extrahilar focal pulmonary calcification develops occasionally [6]. In this patient, elevated ESR and ACE as well as suppressed PTH and their modulation by prednisolone, pulmonary calcification, tuberculin anergy, and steroid-responsive cough, fatigue, weight loss, hypercalcaemia and uraemia, collectively keep the possibility of sarcoidosis in running and rationalize the institution of such therapy.

Reversible components of medical illnesses merit a very high index of suspicion. This subject maintained hypercalcaemia and uraemia despite intensive supportive therapy. The diagnostic dilemma as well as the diabetic status probably delayed the hydrocortisone suppression test for over a year. Progressive/irreversible renal impairment from any other cause might be mistakenly attributed to diabetic nephropathy itself. Sarcoidosis-related hypercalcaemia, regardless of the clinical probability, cannot be excluded without a steroid trial that must be attempted before invasive procedures are envisaged. Hypercalcaemia and its consequences may be managed in sarcoidosis subjects with steroid doses considerably lower than the conventional recommendation (40-60 mg prednisone/day [2]), a particularly significant observation for diabetics. As a reversible cause of renal failure, sarcoidosis – a commonplace multisystem but occasionally subtle clinical syndrome – merits the attention of the nephrologist.

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