Association of medullary sponge kidney disease and multiple endocrine neoplasia type IIA due to RET gene mutation: is there a causal relationship?

Sir,

Medullary sponge kidney disease is a congenital affection, characterized by diffuse ectasy or dilatation of the collecting tubules of one or both kidneys. Its main clinical manifestation is renal stone disease. Its diagnosis is made essentially based on X-ray criteria. Its precise prevalence is not known [1,2]. Its pathogenesis is unknown but most authorities agree that it is a congenital anomaly with delayed expression. It may be associated with other hereditary diseases [1,2]. On the other hand, familial forms have also been described [2,3], and the analysis of various families is in favour of a dominant mode of transmission. The discovery of the gene(s) responsible for this disease would be a great step forward in the understanding of the disease. We describe here the observation of an association between medullary sponge kidney disease, hyperparathyroidism, and medullary thyroid cancer due to a RET gene mutation.

Case. A 36-year-old female patient was admitted to our hospital in March 1997 because of medullary sponge kidney disease, diagnosed by an i.v. pyelography 2 years previously. She had had repeated episodes of urinary tract infection in the years before hospital admission, together with loin pain. She had also undergone an abortion at 8 weeks. She is the mother of three children. She has no hypertension, and the clinical examination revealed no particular signs. The first i.v. pyelography revealed a nephrocalcinosis localized mainly in the area of the pyramids. Complementary examinations showed normal renal function, sterile leukocyturia, a plasma calcium of 13.5 mg/dl, and a serum intact parathyroid hormone (PTH) concentration of 430 pg/ml (normal range 15–65 pg/ml).

Renal ultrasonography confirmed the pyramidal calcifications (Figure 1). A neck ultrasonography showed two images compatible with parathyroid hyperplasia and a left-sided thyroid nodule. Total thyroidectomy and subtotal parathyroidectomy were performed. Histological examination revealed parathyroid hyperplasia and medullary cancer of the thyroid. The patient was subsequently supplemented with oral calcium and thyroid hormones.

A search for genetic markers was done at Edouard Herriot Hospital, Lyon. After amplification by PCR and sequencing of the RET gene, a codon 634 type TGC→TAC mutation on exon 11 was found. The same mutation was detected in two of her three children.

After 40 months of surveillance the patient is doing well. Serum calcium has normalized (9 mg/dl). Similarly serum intact PTH (23 pg/ml) has returned to the normal range. Renal function is normal. However, nephrocalcinosis remains unchanged.

Comment. Multiple endocrine neoplasia type 2A (MEN-2A) is the association of medullary thyroid cancer and primary hyperparathyroidism. Mulligan et al. [4] found a RET gene mutation in 97% of cases with MEN-2A and in 86% of familial medullary thyroid cancer cases. In the case of MEN-2A, 84% of the mutations concern codon 634.

In RET gene knockout mice, the absence of a functional RET protein leads to Hirschsprung’s disease and anomalies of renal embryogenesis [5]. Thus the RET protein is required for the normal development of the urinary excretory system, as well as for that of the enteric nervous system [5]. In addition, during kidney development, RET is expressed in the ureteral bud, which is at the origin of the collecting ducts.

Medullary sponge disease may be associated with several congenital or hereditary diseases, including thyroid hyperplasia and Hirschsprung’s disease [1,3]. However, in most instances, familial medullary sponge kidney disease does not appear to be associated with other disease entities [2].

We believe that the present case is the first description of an association between medullary sponge kidney disease and MEN-2A. The question immediately arises as to whether this is a fortuitous association, or whether there may be a causal relationship. Could it be that the RET gene plays a role in the pathogenesis of medullary sponge kidney disease? Clearly additional studies are required to answer this question.

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