# Detection of Proximal Tubular Motile Cilia in a Patient With Renal Sarcoidosis Associated With Hypercalcemia

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• **In a normal human kidney, almost every cell type gives rise to a solitary primary cilium, an apical hair like nonmotile organelle that recently was linked to the pathogenesis of polycystic kidney disease. Motile cilia normally are not expressed by renal tubular cells in the mammalian kidney. Here, we report the unexpected detection of motile cilia arising from proximal tubular cells in a patient with sarcoidosis associated with hypercalcemia and renal impairment. The possible significance of this unusual finding is discussed.** ***Am J Kidney Dis*** **45:1096-1099.**


**INDEX WORDS: Primary cilia; motile cilia; sarcoidosis; hypercalcemia; polycystic kidney disease.**

CILIA ARE hair like organelles that are expressed ubiquitously. They can be divided into 2 types based on their internal structure: motile cilia are characterized by 9 peripheral doublets of microtubules with a centrally located pair (9 + 2), whereas nonmotile or primary cilia lack the centrally located pair (9 + 0). Motile cilia normally are present as multiple copies arising from each epithelial cell lining such ductal structures as the trachea and fallopian tubes. Conversely, primary cilia are solitary protrusions arising from almost every cell type known.[1] Depending on species, the ultrastructure of renal tubular cilia are either 9 + 0, as in adult human kidney, or 9 + 2, as in invertebrates and lower vertebrates.[2] In the latter, cilia present in the excretory system are clearly motile and thought to contribute significantly to solute and water movement along the nephron. Conversely, primary, or 9 + 0, kidney cilia are not motile, although they can bend in response to flow, and this can lead to an increase in intracellular calcium levels.[3] Here, we report an interesting case in which multiple 9 + 2 cilia arising from proximal tubular cells were observed in the renal biopsy specimen of a patient with sarcoidosis associated with hypercalcemia and renal impairment.

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## CASE REPORT

A 42-year-old man was referred for investigation of impaired renal function discovered incidentally by his general practitioner. On presentation, plasma creatinine level was 4.53 mg/dL (400 μmol/L), plasma calcium level was elevated at 12.9 mg/dL (3.21 mmol/L; normal range, 8.8 to 10.2 mg/dL [2.2 to 2.55 mmol/L]), and parathyroid hormone level was suppressed at less than 2 ng/mL (normal range, 8 to 63 ng/mL). Urinalysis showed protein (+) only. There was evidence of right bundle-branch block and extensive interstitial lung shadowing on electrocardiogram and chest radiograph (Fig 1), respectively. Abdominal radiograph and ultrasound scan showed evidence of nephrocalcinosis. Serum angiotensin-converting enzyme level was elevated at 145 U/mL/min (normal, <52 U/mL/min).

A renal biopsy showed marked interstitial expansion with established fibrosis and a diffuse mononuclear inflammatory cell infiltrate. Possible noncaseating granulomas were identified. Approximately 40% of all tubular profiles were atrophic, with detectable intraluminal nephrocalcinosis in some tubules (Fig 2). Widespread glomerulosclerosis (40%) also was seen, but other glomerular changes were limited to mainly mild mesangial expansion and hypercellularity (Fig 2). No significant immune deposits were seen on immunofluorescence or by means of electron microscopy. An unexpected finding on electron microscopy was the presence of multiple cilia noted to be arising from 2 proximal tubular cells in a single tubular cross-section (Fig 3). Ultrastructurally, these resembled motile cilia with a 9 + 2 instead of 9 + 0 microtubular arrangement (Fig 3B). A diagnosis of sarcoidosis was made, and the patient was started on a decreasing course of oral prednisolone. His latest plasma creatinine and calcium levels while on maintenance oral prednisolone (7.5 mg/d) therapy are 2.17 mg/dL (192 μmol/L) and 9.5 mg/dL (2.36 mmol/L), respectively.

## DISCUSSION

Expression of cilia by the vertebrate kidney or excretory system of invertebrates and lower vertebrates is well documented. In lower organisms,

renal cilia have the classic ultrastructure of motile cilia (9 + 2) and are thought to contribute to the flow of fluid and solute or, possibly, glomerular filtration. However, human fetal and adult metanephric kidneys do not normally express motile cilia.[2] Rather, nonmotile or primary cilia with a typical (9 + 0) ultrastructure are expressed by almost every cell type in the nephron. The precise function of these cilia has been the subject of much interest and speculation by pathologists and anatomists for many decades.[1] More recently, there has been a resurgence of interest in the function of this organelle as the result of genetic studies showing that primary defects in ciliary structure or function probably underlie the pathogenesis of autosomal dominant and autosomal recessive polycystic kidney disease.[4]

The detection of motile cilia arising from proximal tubular cells in our patient was unexpected. Of note, in a single tubule cross-section, not every cell expressed this phenotype, and 2 cells (Fig 3) were found to express solitary nonmotile cilia. Thus, in this (limited) sample, there appeared to be a clear distinction between cells expressing either 9 + 0 or 9 + 2 cilia. Cells from which 9 + 2 cilia were arising, as well as neighboring cells, possessed multiple apical microvilli and numerous mitochondria, features typical of the proximal tubule (Fig 3D). Although calcium deposits were found in several tubular lumina on both light (Fig 2) and electron (not shown) microscopy, we did not observe calcium deposits within this tubular lumen or in the surrounding interstitium.

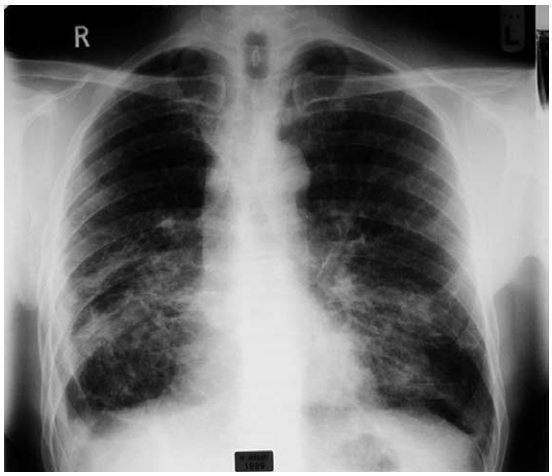


**Fig 1. Chest radiograph shows interstitial shadowing in the midzones of both lungs, typical of sarcoidosis.**

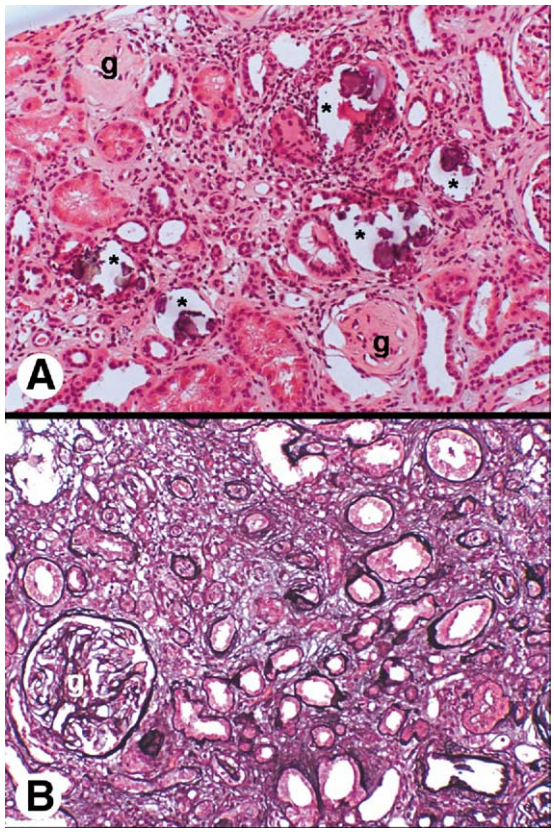


**Fig 2. Light microscopy of a typical cross-section of kidney tissue stained with (A) hematoxylin and eosin or (B) methenamine silver technique. Multiple foci of intraluminal calcium deposits within several tubules that have leached out during tissue processing can be visualized (*). There is marked tubular atrophy, and the interstitium is widely expanded by matrix deposition and inflammatory cells. Forty percent of glomeruli (g) are sclerosed (as shown in A), but the rest show mild mesangial expansion and hypercellularity (as shown in B). (Original magnification ×200.)**

The detection of motile cilia in human kidney is extremely rare, and there appears to be no clear association with a specific disease process. Similar to our patient, a previous study of 60 patients described this appearance in 4 patients with hypercalcemia (3 patients, secondary to milk-alkali syndrome; 1 patient with sarcoidosis).[5] However, this phenotype is not limited to tubular diseases or hypercalciuric states because others have reported a similar appearance in isolated