

## Renal Sarcoidosis Presenting as Fanconi Syndrome

### Published online at

[https://www.acpjournals.org/  
doi/10.7326/aimcc.2022.0140](https://www.acpjournals.org/doi/10.7326/aimcc.2022.0140)

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Publication date: 3 January 2023

### Acknowledgment

The authors thank Dr. Jared Hassler, renal pathologist, for the renal biopsy photograph and Dr. David E. Berman for the 24-hour urine data.

### Disclosures

Disclosure forms are available with the article online.

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### How to Cite

Prakash S, Lu K, Gupta R, et al. Renal sarcoidosis presenting as Fanconi syndrome. *AIM Clinical Cases*. 2023;2:e220140.  
doi:10.7326/aimcc.2022.0140

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### Keywords

*Sarcoidosis, Steroids, Steroid therapy, Nephritis*

### Abstract

Fanconi syndrome is an extremely rare complication of renal sarcoidosis. We describe a case of biopsy-proven granulomatous interstitial nephritis secondary to sarcoidosis with the rare presenting feature of Fanconi syndrome. Our patient successfully received steroids initially, followed by mycophenolate and infliximab. These findings provide clinicians an important insight in recognizing this rare complication of sarcoidosis and opportunity to consider alternative regimens that can avoid or reduce side effects of first-line steroid therapy.

### Background

Renal-limited sarcoidosis is rare, occurring in only 0.5% to 2% of cases (1, 2), and complete Fanconi syndrome secondary to granulomatous nephritis is extremely rare (3). Fanconi syndrome is a dysfunction of the proximal renal tubules, resulting in glycosuria, aminoaciduria, and type 2 renal tubular acidosis (4). In a large case series of patients with renal sarcoidosis, of 47 patients with granulomatous or nongranulomatous interstitial nephritis, only 1 patient (2%) presented with glycosuria, metabolic acidosis, and aminoaciduria (5). In another case series of 24 patients with sarcoid tubulointerstitial nephritis, 9 patients (37.5%) presented with glycosuria (6) but without other features of Fanconi syndrome. A large retrospective analysis of 31 patients with sarcoid-induced granulomatous interstitial nephritis failed to report any cases of Fanconi syndrome (7). To our knowledge, only 3 reported cases of Fanconi syndrome induced by sarcoidosis have been reported, with only 1 reported case of clinical improvement with corticosteroids (1, 2, 8), and no known reported cases of treatment success with alternative regimens. Rarity of this condition requires a high index of suspicion and low threshold for workup for accurate diagnosis and subsequent treatment and follow-up.

### Objective

We describe a case of secondary Fanconi syndrome confirmed with urine studies. Mycophenolate and infliximab, considered steroid-sparing and alternative therapy, respectively, were beneficial when steroids elicited intolerable side effects.

### Case Presentation

A 48-year-old African American woman was admitted with marked hypercalcemia and impaired renal function. Her only symptom was unexpected weight loss over 3 months. She did not report pulmonary, cardiac, or gastrointestinal symptoms.

Her medical history was significant for diabetes, which she developed after an episode of acute pancreatitis 2 months prior, hypertension, and remote stroke. Her home medications included carvedilol, baby aspirin, simvastatin, ergocalciferol, and insulin twice daily. Her family history was significant for a maternal aunt with multiple myeloma. Physical examination revealed a moderately obese female with normal vital signs. Her chest was clear, heart sounds were normal, jugular venous pressure was not elevated, and abdominal examination was unremarkable. There was a trace of peripheral edema below the knees bilaterally.



**Table 1.** Serum Laboratory Results Before and After Volume Resuscitation and After Medical Therapy for Sarcoidosis

Laboratory Test Results	Reference Range	Admission	After Volume Resuscitation	After 9 Months	After 36 Months
Glucose, mmol/L	3.3–5.5	13.1	9.8	9.5	38.3
Sodium, mmol/L	136–145	136	144	145	130
Potassium, mmol/L	3.5–5.2	3.2	3.1	4.2	5.1
Chloride, mmol/L	101–111	106	118	107	94
Bicarbonate, mmol/L	22–32	21	17	18	20
Blood urea nitrogen, mmol/L	2.8–7.14	15	5	8.2	13.6
Creatinine, umol/L	53–97.2	189	159	141.4	150
Calcium, mmol/L	2.15–2.5	3.7	3	2.6	2.4
Ionized calcium, mmol/L	1.15–1.3	1.9	–	1.5	–
Hemoglobin, g/L	120–160	124	98	120	115
Intact PTH, ng/L	14–72	22	–	89	161
PTH-RP, ng/L	14–27	13	–	–	–
Albumin, g/dL	35–50	35	–	41	–
Magnesium, mmol/L	0.66–1.07	0.78	0.7	0.99	0.95
Phosphorus, mmol/L	0.78–1.42	0.48	0.48	0.81	0.95
Beta 2 microglobulin, mg/L	1.16–2.52	8.53	–	–	–
Vitamin D 25, nmol/L	74.8–249.6	59.9	–	34.9	54.4
Vitamin D 1,25, pmol/L	43.2–172.8	79.2	–	79.2	–
Angiotensin-converting enzyme level, nkat/L	150–1116.7	950	–	150	–

PTH = parathyroid hormone; RP = related protein.

Admission laboratory values were the first set of serum investigations on admission, after volume resuscitation laboratory tests were done later the same day after intravenous normal saline resuscitation. The investigations at 9 months were done on low-dose prednisone, mycophenolate mofetil, and hydroxychloroquine. The laboratory investigations after 36 months were done after she was induced with infliximab, mycophenolate mofetil, and low-dose prednisone and withdrawn from the mycophenolate. – = where data were not available or measured.

Her initial laboratory investigations (Table 1) were notable for a creatinine of 189 umol/L, calcium 3.7 mmol/L, intact parathyroid hormone of 22 ng/L, 25-vitamin D was 59.9 nmol/L, 1,25 vitamin D pmol/L, and hemoglobin 124 g/L. Repeat laboratory values were obtained after volume resuscitation and revealed potassium of 3.1 mmol/L, bicarbonate 17 mmol/L, sodium 144 mmol/L, chloride 118 mmol/L, creatinine 159 umol/L, urea 5 mmol/L, calcium 3 mmol/L, magnesium 0.7 mmol/L, and phosphorus 0.48 mmol/L. Hemoglobin was 98 g/L. Chest X-ray 1 day after admission was normal.

Initial management focused on treatment of her hypercalcemia: Ergocalciferol was stopped, and her volume depletion was treated with intravascular (IV) normal saline. She received IV pamidronate, intramuscular calcitonin, and aggressive repletion of her electrolytes, including potassium, magnesium, and phosphorus. Workup for secondary causes of hypercalcemia eliminated other causes, including primary hyperparathyroidism, humoral hypercalcemia of malignancy, and multiple myeloma. The 24-hour urine level was significant for 38.9 mmol of magnesium, phosphorus 6750.7 mmol, glucose 54.7 mmol, and elevated levels of the amino acids hydroxyproline, citrulline, proline, alpha amino butyric acid, valine, homocysteine, and cysteine, which is consistent with Fanconi syndrome (Table 2). Urinalysis by dipstick showed pH of 5.5, no blood, protein was 1+, and glucose was elevated. Serum angiotensin-converting enzyme level was normal at 950 nkat/L. Renal biopsy was performed and showed a multinucleated giant cell present in the interstitium, interstitial nephritis, and noncaseating granulomas, consistent with renal sarcoidosis (Figure 1).

She initially received oral prednisone at 50 mg daily with a plan to continue for 2 months and withdraw. She no longer required electrolyte supplementation at 1 month, reflecting a successful response of her Fanconi syndrome. However, at 5 weeks, prednisone was withdrawn and then resumed at the reduced dosage of 20 mg after she developed a perianal abscess. Over the course of the next several months, in an effort to wean prednisone, she was started on hydroxychloroquine 200 mg twice daily and mycophenolate 500 mg twice daily. Frustrated with recurring side effects, she self-discontinued all her immunosuppressive medications, leading to readmission at 14 months after diagnosis with a serum calcium of 3.3 mmol/L. She received infliximab 600 mg, mycophenolate 1 g twice daily, and prednisone 2.5 mg daily, to which she responded appropriately. Eventually, mycophenolate was withdrawn, and monthly infliximab was successfully continued in addition to low-dose prednisone for maintenance therapy.

### Discussion

Our patient presented with Fanconi syndrome, a rare complication of renal sarcoidosis, characterized by impaired proximal tubule dysfunction. The mechanism by which patients develop dysfunction of proximal renal tubules with resultant glycosuria, aminoaciduria, and type 2 renal tubular acidosis is not well-defined. Possible mechanisms include widespread abnormalities of most or all of the proximal tubule carriers, “leaky” brush border or basolateral cell membrane, inhibited or abnormal sodium-potassium-ATPase pump, impaired mitochondrial energy generation, or other cell organelle dysfunction (4). Our patient’s urine studies demonstrated elevated levels of protein, amino acids, glucose, and electrolytes, confirming the diagnosis.

**Table 2.** The 24-hour Urine Results Showing Initial Fanconi Syndrome and Improvement After Sarcoidosis Treatment

Laboratory Test	Reference Range	Initial Results	After 2 Months of Prednisone
Total volume, L		3.7	2.2
Protein, mg	<150	1036	221
Magnesium, mmol	−3–5	38.9	–
Phosphorus, mmol	12.9–42	6750.7	19.4
Glucose, mmol	<2.78	54.7	
Creatinine, mmol	9.78–17.72	12.99	10.95
Calcium, mmol	2.5–7.5	10.2	2.28
Hydroxyproline, mmol/mol creatinine	≤2	6	–
Citrulline, mmol/mol creatinine	≤2	10	–
Proline, mmol/mol creatinine	≤2	11	–
α-Amino butyric acid, mmol/mol creatinine	≤2	3	–
Valine, mmol/mol creatinine	2.0–5.0	10	–

The normal range for 24-hour urine creatinine listed is calculated from the patient's weight of 100.1 kg and uses the normal range for adult females (97.7–177 μmol/kg/24 hours). The initial results were from 1 day after the initial hospital admission described in this report; the after 2 months of prednisone column was after 5 weeks of high-dose steroids and 3 weeks of lower dose steroids. – = where data were not available or measured at that time. All values listed are the total amount in 24 hours.

\*The urinary phosphorus result is markedly elevated. Additional steps were taken to verify its accuracy, including an assessment of the instrumentation with the manufacturer, use of laboratory controls, and consideration of human data entry error. Review of all these factors made error highly unlikely. Rarely, the phosphorus assay can be affected by other proteins in the sample, and we could not completely exclude some degree of protein artifact causing an elevated level. However, in line with the patient's clinical presentation, we believe this markedly elevated phosphorus level represents a true value.

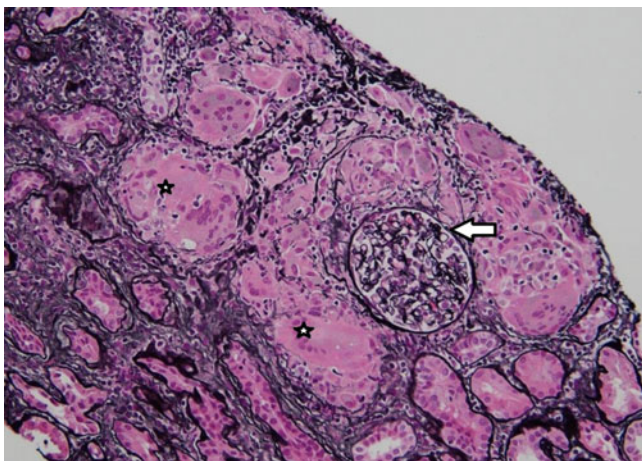
Of note, her urine phosphate level was markedly elevated; a similar degree of elevation could not be found in the literature. Additional steps were taken to verify and confirm the level's accuracy. In line with the patient's clinical presentation, it was believed that the markedly elevated phosphorus represented a true value, with subsequent normalization after treatment.

In addition to Fanconi syndrome, our patient presented with hypercalcemia, which is more common in patients with granulomatous disease. In accordance with published reports, vitamin D replacement was discontinued (9), and our patient received corticosteroids with subsequent resolution of her electrolyte and renal abnormalities. Corticosteroids have been shown to be effective with secondary Fanconi syndrome (2). However, alternative therapies needed to be considered once she developed intolerable side effects. Alternative regimens used in sarcoidosis

include antimalarial and cytotoxic drugs such as azathioprine, cyclophosphamide, and methotrexate (10). There is evidence for successful management of renal-limited sarcoid with mycophenolate mofetil (11), which was attempted but then had to be discontinued because of side effects. Infliximab, a third-line agent for sarcoidosis, is a tumor necrosis factor-α inhibitor and is generally reserved for treatment of patients with persistent sarcoidosis disease who have failed treatment with glucocorticoids and at least 1 steroid-sparing agent (12). Stabilization of glomerular filtration rate has been reported in 1 case of renal-limited sarcoidosis treated with infliximab refractory to steroid therapy (13), but there are no reported cases of renal-limited Fanconi syndrome treated with these therapies. Our patient's Fanconi syndrome remained successfully treated with infliximab, as evidenced by normalization of serum potassium, phosphorus, and calcium values, and she was maintained on infliximab and low-dose prednisone. Our patient case describes a presentation of Fanconi syndrome secondary to renal sarcoidosis. Recognition of this rare condition requires a high index of suspicion and low threshold of pursuing diagnostic studies. Alternative immunosuppressive therapies should be considered when first-line agents are not an option.

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**Figure 1.** Renal biopsy (Jones Silver stain; original magnification ×20). A glomerulus is seen just right of center with a Bowman's capsule outlined by the stain (arrow) and surrounded by noncaseating granulomata (stars).

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