Case Report

Severe hypercalcemia in nonobstructive pyelonephritis with acute renal failure: hit or miss?

Abstract

Severe hypercalcemia in the course of renal failure is quite unusual. If unrecognized, irreversible inexorable attrition of renal function takes place, carrying a substantial morbidity and mortality. In particular, acute nonobstructive pyelonephritis is barely considered in the primary differential diagnosis of renal failure. Without urinary obstruction, kidney hypoperfusion, or exposure to nephrotoxic agents, a significant decline in glomerular filtration rate generally does not occur. We report a case with severe hypercalcemia after acute renal failure caused by fulminating bacterial pyelonephritis. To obviate unnecessary intervention, preserve organ function, and achieve better outcomes, clinicians should not miss this entity.

A previously healthy 58-year-old woman with acute pyelonephritis was referred to the emergency department for the evaluation and management of acute renal failure. She had flank pain on both sides and fever with rigor waxed and waned in the past 5 days. Oliguria developed and became prominent in the 24 hours before coming to the hospital. Upon examination, she was obtunded, and her blood pressure was 156/88 mm Hg; heart rate, 86 beats per minute; respiratory rate, 18 breaths per minute; and body temperature, 38.8°C. Laboratory studies showed hemoglobin level of 12.8 g/dL, platelets of 315 × 10⁹/L, and leukocytes of 19.5 × 10⁹/L with a left shift; serum biochemistries revealed hyperkalemia (7.2 mmol/L), hypercalcemia (ionized calcium, 7.9 mg/dL), hyperphosphatemia (6.4 mg/dL), and acute renal failure (blood urea nitrogen, 87 mg/dL; creatinine, 8.3 mg/dL). Urinalysis showed 30 to 40 leukocytes per high-power field with few white blood cell casts and fine granular casts. Renal ultrasonography showed mild enlarged kidneys with poor-defined corticomedullary differentiation, indicating bilateral nonobstructive pyelonephritis. Hemodialysis was started immediately, and after 6 sessions, recovery of renal function, signaled by brisk diuresis, occurred. A systematic approach prompted further evaluation focused on absorptive hypercalcemia (Fig. 1), as evidenced by hypercalciuria (fraction excretion of calcium, 3.6%), a high serum concentration of 1,25(OH)₂D₃ (183 pmol/L) and suppressed intact parathyroid hormone (4.1 pg/mL), and undetectable parathyroid hormone–related peptide. In view of uncertainty of acute kidney injury, a biopsy of the left kidney disclosed normal glomeruli, severe interstitial neutrophilic infiltration, and edema with no signs of acute tubular necrosis. Cultures from urine and blood all grew Escherichia coli. Intravenous administration of cefepime for consecutive 2 weeks achieved a gradual recovery. At a 3-month follow-up, she was normocalcemic with only mildly compromised renal function.

Acute pyelonephritis (APN) is a serious infection of the upper urinary tract requiring prompt and thorough clinical assessment. In general, risk factors for complicated APN include pregnancy, diabetes, anatomical abnormalities of the urinary tract, renal calculi, neuropathic bladder, transplant recipient, and immunosuppressed state [1]. However, even in APN with marked septicemia, acute renal failure rarely occurs if there is no concomitant urinary tract obstruction, kidney hypoperfusion, or exposure to nephrotoxic agents [2]. Usually, a significant impairment of global renal function does not prevail in APN because there is only focal, lobar involvement of the kidneys and there are still enough functioning nephrons to compensate for the damaged renal parenchyma. In fact, the effects of APN on kidney function are mild and may limit to a transient loss of concentrating ability.

Although the pathogenetic basis remains unclear, the disruption of tubular function by interstitial infiltrates of neutrophils and phagocytes, interstitial edema, tubular obstruction by cellular debris, and intrarenal vasoconstriction have been described as possible etiologies of acute renal failure in nonobstructive APN [3]. The neutrophil and the local environment of cytokine/chemokine/cell adhesion molecules govern the intensity and persistence of the host response during APN. Genetic variability in the function of the host immune system as mirrored in single nucleotide polymorphisms in cytokines, cytokine receptors, chemokines, and cell adhesion molecules may explain the interindividual variability in cellular response reflected by different clinical outcomes [4]. Of interest, an acute reduction of glomerular filtration rate may be a surrogate for the severity of APN and thereby portends a delayed recuperation, although uncertainty exists as to whether glomerulopathy or tubulopathy predominates.
**Hypercalcemia**

![Hypercalcemia Diagram](image)

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**E. coli** is the pathogen most often involved and causes greater than 80% of community-acquired urinary tract infection. In our patient, both urine and blood cultures grew an *E. coli* strain (serotype O4:H51), which harbored an acquired, class A, β-lactamase. Polymerase chain reaction analyses revealed that the *E. coli* strain isolated from the urine contained multiple virulence factors of extraintestinal pathogenic *E. coli* (type 1, P and S fimbriae, aerobactin, and cytotoxic necrotizing factor type 1) that belonged to group B2, suggesting that it was a member of a specific clone with urovirulence. Consistent with these data, there was no detected virulence factor associated with the intestinal *E. coli* strains in the studied isolate. Although the *E. coli* isolate identified from the host clinical specimen exhibited features of uropathogenic *E. coli* clones, the identified virulence factors could not fully account for the severity of acute kidney injury. Therefore, it is tempting to speculate that this uropathogenic strain may exhibit potent invasive capacities with rapid hematogenous spreading and induce inordinate inflammatory reactions responsible for the development of acute renal failure.

Although hypercalcemia per se seems to play a permissive role in acute renal failure of our patient, its basis arising from vitamin D–related absorptive nature is quite important. In fact, the role of vitamin D extends well beyond that of regulating calcium homeostasis, and one of these areas is immune function. Overproduction of active 1,25(OH)2D3 caused by increased macrophagic 1α-hydroxylase activity in granulomatous lesions can provoke a disruption of mineral homeostasis [6]. Of note, the activation of macrophages through toll-like receptors is considered to be a key mechanism in immune abnormalities associated with sepsis/systemic inflammatory response syndrome. Toll-like receptor activation of human macrophages can up-regulate the expression of vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular mycobacterium infection [7]. Conceivably, 1,25(OH)2D3 produced by macrophages probably has only a local effect in sustaining cell-mediated immunity and should not normally affect calcium metabolism [8]. However, if large quantities of 1,25(OH)2D3 are produced through an undefined mechanism, “overspill” into the circulation can occur, resulting in marked hypercalcemia.

The management of acute kidney injury is a fairly common scenario in emergency practice, but occasionally, it can be quite challenging as muddled by missed complexity. The case reinforces the need for clinicians to maintain awareness of this condition, and better outcomes only rely on early identifying the etiology followed by expeditious intervention.
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