Amoxicillin-induced crystal nephropathy, a crystal clear cause of acute kidney injury during treatment for infective endocarditis: a case report

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ABSTRACT

Background: Amoxicillin, a commonly used broad-spectrum antibiotic, can crystallize in renal tubules when administered at high doses, causing acute amoxicillin-induced crystal nephropathy (AICN). This condition typically presents with acute kidney injury (AKI) and macroscopic hematuria. Risk factors include high dosage, rapid infusion, dehydration, and low urinary pH. Although urine microscopy can confirm amoxicillin crystals (AC), it is underutilized, contributing to under recognition of AICN.

Case Report: We present the case of a 75-year-old woman with fever and cellulitis, diagnosed with native aortic valve endocarditis due to *Streptococcus dysgalactiae*. She was treated with high-dose intravenous amoxicillin (6 × 2 g/day). On day two, she developed macroscopic hematuria and progressive AKI, eventually requiring temporary hemodialysis. Urine microscopy revealed elongated AC, confirming the diagnosis of AICN. Amoxicillin was discontinued and replaced with continuous penicillin G infusion. Renal function recovered markedly within 1 week, allowing discontinuation of dialysis.

Discussion: This case highlights the importance of considering AICN in patients receiving high-dose amoxicillin who develop unexplained AKI and hematuria. Urine microscopy is a valuable, non-invasive diagnostic tool and should be more routinely used in suspected cases to enable early detection. Timely diagnosis through urine microscopy is crucial, as discontinuation of amoxicillin can lead to rapid and complete renal recovery.

Keywords: Amoxicillin-induced crystal nephropathy (AICN), high-dose amoxicillin therapy, adverse drug effect, crystalluria; urine microscopy, case report.

Type of Article: CASE REPORT **Specialty:** Nephrology

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Background

Crystalluria is a common finding in standard urine sampling [1]. Among them, only a minority of cases are caused by pathological conditions or by drugs that can crystallize in the tubular lumina, leading to renal damage [1]. One of those drugs is amoxicillin, a widely used antibiotic because of its broad-spectrum mechanism. Amoxicillin crystals (AC) are diagnosed by detecting amoxicillin trihydrate crystals in urine, typically elongated needle-shaped [2]. This may lead to acute amoxicillin-induced crystal nephropathy (AICN), which is usually described as the sudden onset of macroscopic hematuria together with oligo/-anuria and a rise in creatinine level, i.e., acute kidney injury (AKI) grade 2-3 according to the KDIGO guidelines, in patients receiving high dose Amoxicillin (≥150 mg/kg per day) [2-5].

Although urine microscopy provides a simple and direct method for identifying AC, it is rarely performed in practice due to technical and practical constraints [6]. Therefore, different diagnostic criteria were used in previous studies, with most of them only using the co-incidence of high dose Amoxicillin administration, AKI, and micro-/macroscopic hematuria, in addition to ruling out other possible causes of AKI, as sufficient to make the diagnosis of AICN [3,6,7].

The lack of standardized diagnostic criteria, along with the absence of routine use of urine microscopy, partially explains the uncertainty existing about the incidence of AICN [3]. Recent studies did show a notably increase since 2010 in France [3,6,7]. The authors of these studies hypothesized that the rise in reported cases of AICN may be attributed to previous underreporting of the complication, combined with increased awareness among clinicians, so the true incidence still remains unknown [1,2,8,9].

AICN occurs due to the obstruction of the ureter and/or renal tubules by AC [7]. It is thought to be related to a concentration-dependent oversaturation of amoxicillin and subsequent crystallization in the urine following glomerular filtration and tubular secretion of amoxicillin [1,10]. Risk factors for the crystallization and tubular deposition of amoxicillin are related to the pathophysiology and include administration of high doses (> 12 g/d), rapid infusion (> 2 g/30 min), oliguria, dehydration, hypovolemia, and low urinary pH [10,11].

Treatment consists of discontinuation of amoxicillin treatment and improving tubular flow and urine output with volume resuscitation [2]. About 70%-80% of the patients developing AC experience renal failure [11]. However, the prognosis is mostly favorable, and patients generally recover to normal kidney function 3-17 days

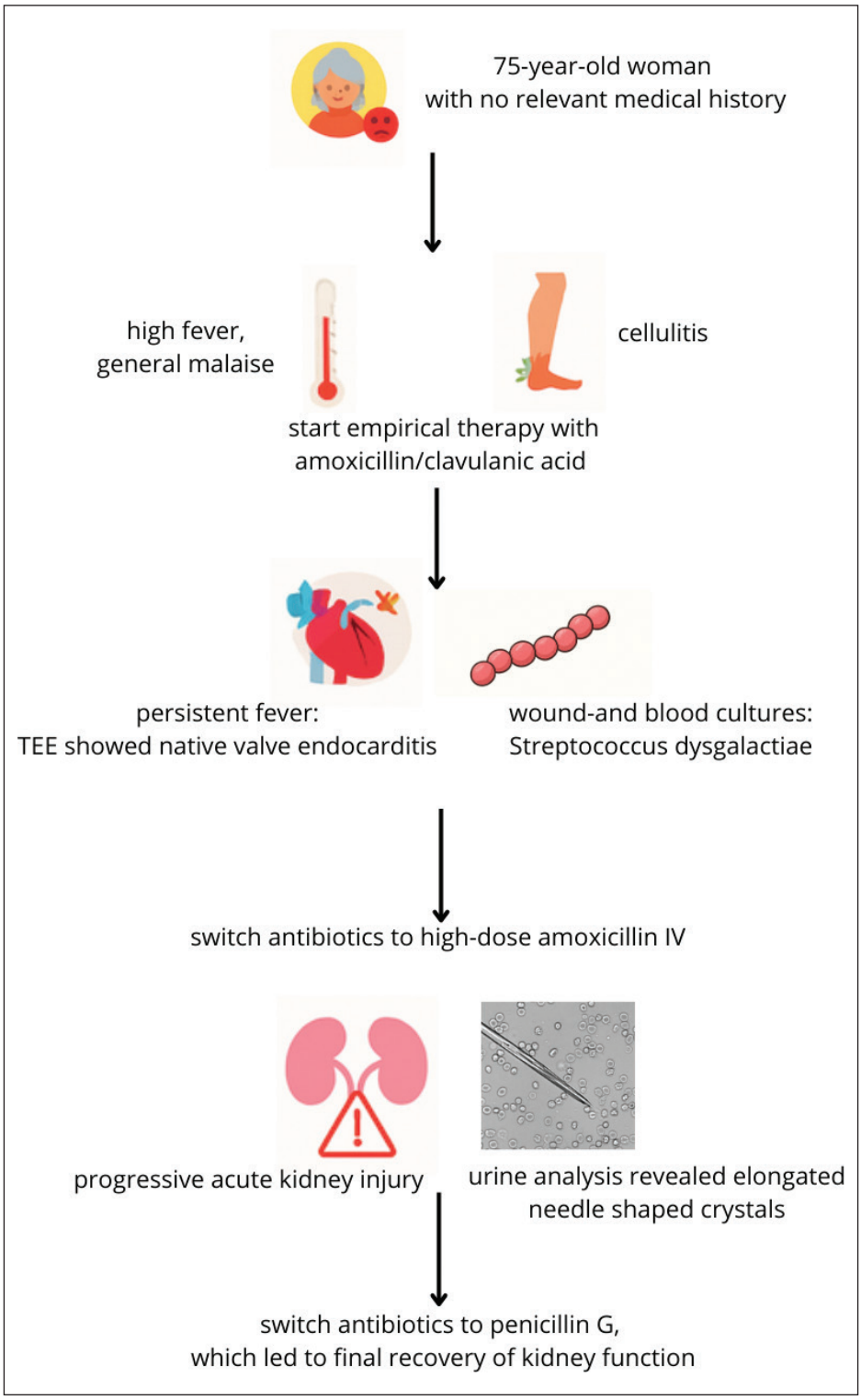

Figure 1. *Schematic overview of case.*

after stopping amoxicillin [1,2,10]. Still, temporary renal replacement therapy is needed in 10%-40% of patients [2].

Case Description

A 75-year-old woman with no relevant medical history presented herself to the emergency department with high fever and general malaise (Figure 1). She reported several days of poor appetite and a dry mouth, with complete absence of oral intake. In particular, she did not recognize that she had a fever. She denied respiratory, gastrointestinal, or urinary symptoms. Her left leg, which had long-standing varicose veins, showed new-onset redness and was painful to touch. On clinical examination, her vital signs were notable for a fever of 40.2°C. She was hemodynamically stable. Cardiac exam revealed no murmurs, but she was tachycardic with jugular venous distension. Lung auscultation and abdominal examination were normal. Lower extremities exhibited bilateral pitting edema, more pronounced on the left, with erythema and tenderness. Neurological examination was unremarkable.

Initial work-up and bedside ultrasound suggested extensive cellulitis of the left lower leg without evidence of deep vein thrombosis. Other initial investigations (e.g., X-ray of chest, abdominal ultrasound) were negative, so at that time the cellulitis seemed to be the only identifiable focus of fever. Empiric intravenous amoxicillin/clavulanic acid was initiated in combination with IV hypotonic fluids because of the absence of oral intake. Blood cultures later yielded *Streptococcus dysgalactiae*, which was also isolated from a wound culture from the affected leg. Due to persistent fever, a transesophageal echocardiogram (TEE) was performed, which confirmed native aortic valve endocarditis with vegetations on the non-coronary cusp. In line with the 2023 European Society of Cardiology guidelines, antibiotic therapy was adjusted to high-dose IV amoxicillin (6 × 2 g/day) [12]. In addition, the TEE confirmed intravascular underfilling, for which the ongoing hypotonic intravenous fluid infusion rate was increased.

Two days later, the patient developed progressive AKI, with macroscopic hematuria and non-nephrotic range proteinuria. Urinary pH was in the low-normal range. Initial differential diagnosis included prerenal kidney injury given the intravascular underfilling on TEE, acute tubular necrosis possibly linked to a short hypotensive episode, sepsis-induced AKI, acute interstitial nephritis (**AIN)** secondary to antibiotic exposure, septic emboli, and peri-infectious glomerulonephritis. Despite supportive care - including adjustment of the intravenous fluid infusion rate and administration of sodium bicarbonate - the renal function deteriorated further, necessitating acute hemodialysis.

The differential diagnosis was approached as followed: prerenal kidney injury became less likely after correct fluid resuscitation failed to improve kidney function. Sepsis-induced AKI was not favored, as macroscopic hematuria is uncommon in this condition. AIN was deemed less likely, given the early onset of AKI after amoxicillin exposure. Embolic phenomena were unlikely, since clinically significant renal dysfunction would require bilateral involvement,

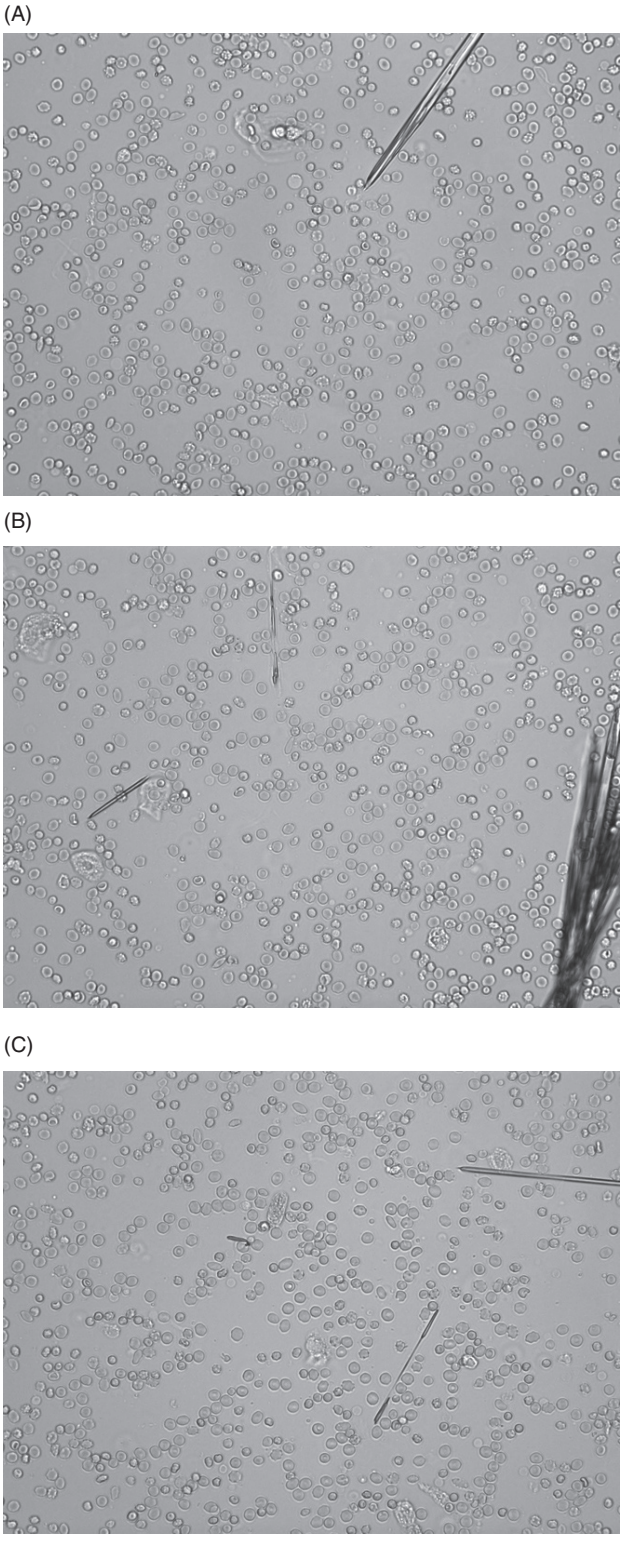

Figure 2. *Digital light microscopy (Atellica UAS8000 of Siemens Healthineers) revealing amoxicillin crystals: needle-shaped elongated crystals A: Digital light microscopy (Atellica UAS800 of Siemens Healthineers) revealing AC: a needle-shaped elongated crystal. B: Digital light microscopy (Atellica UAS800 of Siemens Healthineers) revealing AC: two needle-shaped elongated crystals and large aggregated needle-shaped crystals. C: Digital light microscopy (Atellica UAS800 of Siemens Healthineers) revealing AC: two needle-shaped elongated crystals.*

which is rather uncommon. Eventually, the main diagnostic challenge remained distinguishing peri-infectious glomerulonephritis from possible crystal nephropathy.

Given this uncertainty and the further deterioration of kidney function, urine microscopy was repeated 4 days after the onset of AKI, revealing the presence of elongated crystals, which confirmed the diagnosis of AICN (Figure 2A-C). Amoxicillin was discontinued and changed to Penicillin G in continuous infusion. After discontinuation of amoxicillin in favor of intravenous penicillin, the kidney function improved rapidly within the next 7 days and eventually returned to baseline (Figure 3). This rapid improvement of renal function also ruled out acute tubular necrosis as the cause of AKI. Additional renal biopsy was considered obsolete, given its invasiveness, bleeding risk, and the prior confirmation of typical AC along with rapid improvement after drug withdrawal. Consequently, temporary hemodialysis was fully withdrawn after several days (Figure 4 – timeline).

Follow-up echocardiography at 2 weeks showed stable non-progressive aortic insufficiency, with persistent vegetations on the aortic valve, indication for a further conservative approach. After 4 weeks of intravenous antibiotic treatment, nevertheless, she developed progressive aortic regurgitation necessitating aortic valve replacement. Renal function remained stable during this period, and monthly follow-up over 1 year after discharge confirmed persistently normal values.

Discussion

AICN is an under recognized, but important complication of a commonly prescribed antibiotic. Our patient had several recognized risk factors for AICN, including high-dose amoxicillin, dehydration, and poor oral intake. Preventive measures such as the administration of intravenous hypotonic maintenance fluids and adjusting the infusion rate in response to intravascular underfilling on TEE were implemented before the onset of AKI, while urine alkalinization was initiated after AKI-onset. In retrospect, optimization of intravascular volume in the context of hypotension and persistent intravascular underfilling might have been better achieved by adding isotonic resuscitation fluids rather than simply increasing the infusion rate of hypotonic maintenance fluids. This better management of hypovolemia could potentially have reduced the severity of acute renal injury.

Although historically considered rare, different studies now suggest an increase in the incidence of AICN [3,6,7].

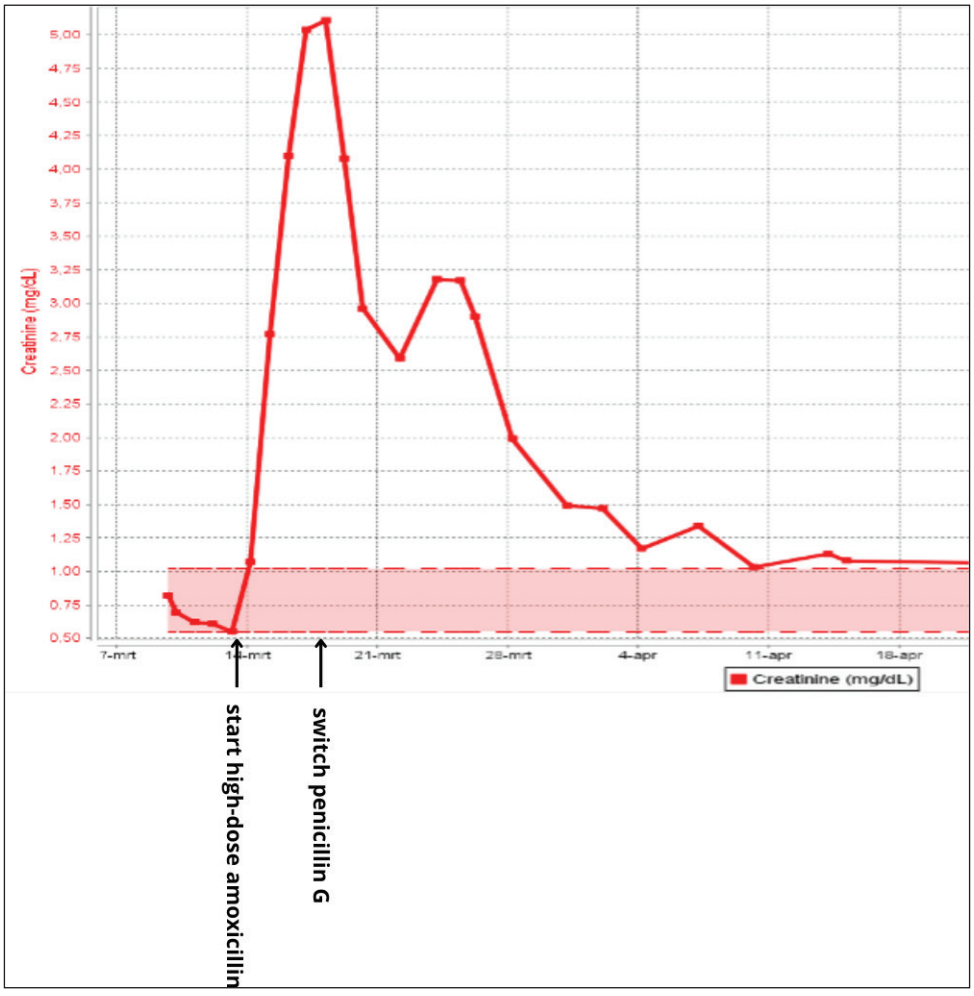

Figure 3. *Serum creatinine as a function of time.*

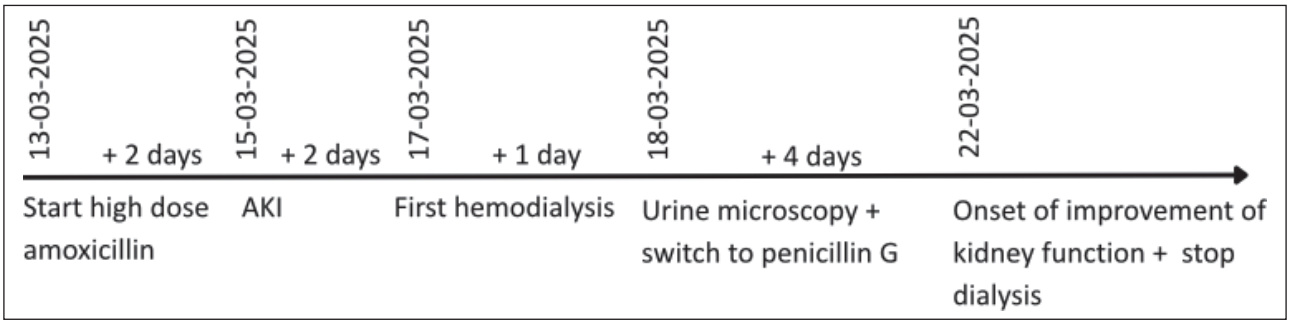

Figure 4. *Timetable summarizing antibiotic exposure, onset of AKI, timing of urine microscopy, dialysis and recovery.*

The potential impact of reporting bias and increased awareness on this rise in reports should, however, be acknowledged, given the fact that the most recent data come from pharmacovigilance studies conducted in France. Thus, its true incidence remains unclear, also considering the absence of standardized diagnostic criteria and underuse of crystal identification through urine microscopy [3,6,7]. The pharmacovigilance studies propose three criteria for the diagnosis of AICN - AKI, temporal association with amoxicillin use, and micro- or macroscopic hematuria [3,6,7]. However, these criteria have limitations: hematuria is not consistently present, and the concept of 'temporal association' is poorly defined, as AKI may develop immediately or several days after initiation of treatment. Moreover, it makes it difficult to differentiate from infectious glomerulonephritis, which would also present with (albeit glomerular) hematuria and AKI in temporal association with infection (and thus antibiotic use).

Another complicating factor in diagnosing AICN is the differential diagnosis with sepsis-induced AKI and AIN. Sepsis-induced AKI often poses the greatest diagnostic challenge in infectious contexts due to the lack of specific biomarkers distinguishing it from other forms of AKI [2]. It is typically accompanied by dysfunction of at least one other organ system and usually develops within 7 days of sepsis onset [2]. In contrast, AIN represents a hypersensitivity reaction frequently triggered by drugs such as amoxicillin, generally occurring after a longer latency (>10 days) and may rarely be accompanied by fever, rash, and arthralgia [9]. It should be suspected in patients with rising serum creatinine and urinalysis showing white blood cells, white cell casts, or eosinophiluria, although urinary findings may be minimal [13]. Recovery from AIN is typically slower than from AICN, and a definitive diagnosis of either condition requires a kidney biopsy [2,9].

In clinical practice, biopsy is rarely performed if the diagnosis for underlying AKI is strongly supported by clinical context, if renal function improves after stopping the suspected drug, and if urine microscopy provides sufficient evidence when typical needle-shaped crystals are identified. All three conditions were present in this case, supporting a presumptive but well-supported diagnosis of AICN [7].

Although urine microscopy is widely available, reliable detection of AC requires prompt examination of fresh urine with polarized light microscopy and operator expertise, as the characteristic needle- or rod-like crystals can be easily missed. False negatives are common, particularly with delayed processing, transient crystalluria, anuria, crystal dissolution in alkaline urine, or milder cases. Nonetheless, urine microscopy remains a rapid diagnostic tool, especially when the lack of adequate diagnosis could cause a delay in appropriate therapy [14].

This case report is relevant as it highlights a relatively rare but important complication of a commonly used drug. It illustrates that even with limited diagnostics, the diagnosis of AICN can be confidently made, allowing for prompt intervention and rapid reversal of AKI. A key component in this process is urine microscopy, which can detect AC and aid in differentiating AICN from other conditions, as demonstrated in this case report. Nonetheless, as a single-case report, its findings remain inherently limited and cannot be generalized.

Conclusion

AICN is an unusual but potentially severe complication of high-dose intravenous amoxicillin. This case demonstrates that in the presence of a broad differential diagnosis, the detection of typical urinary crystals through urine microscopy, together with the temporal relationship between amoxicillin use and AKI, can provide sufficient diagnostic confidence, without the need for invasive testing. Confirmation of AC via urine microscopy was the key element in guiding timely therapeutic decisions. Early recognition facilitated by urine microscopy is crucial, as discontinuation of amoxicillin usually leads to rapid and complete renal recovery.

What is new?

This case emphasizes the importance of urine microscopy as a rapid, non-invasive, and accessible diagnostic tool for AICN, providing clear evidence that may avoid the need for kidney biopsy. The detection of characteristic amoxicillin crystals allows clinicians to narrow a broad differential diagnosis and guide immediate, appropriate therapeutic interventions, supporting the value of its routine use in the evaluation of acute kidney injury during amoxicillin treatment.

List of Abbreviations

AC	Amoxicillin-crystals
AICN	Amoxicillin-induced crystal nephropathy
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
TEE	Transesophageal echocardiogram

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding

None.

Consent for publication

The patient provided written informed consent for the publication of the clinical details and any associated images included in this case report.

Ethical approval

The Ethics Committee of the General Hospital AZ Sint-Lucas Brugge raised no objection to publication. Ethical approval date: 06-10-2025; letter number AZSTL2025-013.

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Summary of the case

1	**Patient (gender, age)**	Woman, 75 years old
2	**Final diagnosis**	Amoxicillin-induced crystal nephropathy
3	**Symptoms**	General malaise, fever and painfully swollen lower left leg
4	**Medications**	Amoxicillin high dose, after diagnosis changed to Penicillin G
5	**Clinical procedure**	Urine analysis revealing elongated crystals. Discontinution of Amoxicillin and switch to Penicillin G.
6	**Specialty**	Internal medicine