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Dr. Koushiki Bhattacharjee
Junior Resident, Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

Dr. Varun Kumar Singh
Assistant Professor, Pathology, Melaka Manipal Medical College, Manipal campus, Manipal Academy of Higher Education, Manipal, Karnataka, India

Dr. Sushma Belurkar
Associate Professor, Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

Corresponding Author:
Dr. Varun Kumar Singh
Assistant Professor, Pathology, Melaka Manipal Medical College, Manipal campus, Manipal Academy of Higher Education, Manipal, Karnataka, India

Unexpected crystalluria: Report of three cases

Koushiki Bhattacharjee, Varun Kumar Singh and Sushma Belurkar

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Abstract
Detection and reporting of crystals in urine is an integral part of a clinical laboratory. Presence of crystals is not always pathological and affected by a variety of pre analytical factors. Pathologically significant crystals are rare and seen in acidic urine. Here we report three such cases where urine crystals posed a reporting dilemma. Case 1: 3-year-old male child with nephrotic syndrome showed thorn apple shaped ammonium biurate crystals in urine with pH 6.8. Ammonium biurate crystals are seen in alkaline urine and this scenario of slightly acidic urine and background of nephrotic syndrome is a usual one. Case 2: 10-year-old male with fever, jaundice and hepatomegaly showed a urine pH of 5.6 and yellow round leucine crystals with radiating striations. Leucine crystals are indicative of severe liver damage and the child was found to have chronic Hepatitis B infection. Case 3: 35-year-old female with generalised weakness and prutitis, showed a urine pH of 6 and fine needle like clusters of bilirubin crystals. These crystals are rare and occur in background of severe hyperbiliribinemia, the patient was found to have a carcinoma involving head of pancreas. Morphology, solubility testing with organic/mineral acids and alkali aids in diagnosis under unexpected scenarios.

Keywords: Crystalluria, crystals, clinical laboratory

Introduction
Urine examination is one of the first investigations done in a clinical laboratory, as a panel of baseline investigations. Crystalluria often is an indicator of a diseased state indicating organ dysfunction, urolithiasis, or a urinary tract infection. Presence of crystals is not always pathological and affected by a variety of pre analytical factors [1, 2]. Fogazzi *et al*. [3] noted that 8% of the specimens examined in his laboratory showed crystals. Pathologically significant crystals are rare and seen in acidic urine. Crystals in the freshly voided urine sample suggest an *in vivo* crystal formation, which is deleterious for renal tubular functions warranting special care while reporting them [4]. We here report a case series of four cases where urine crystals posed a reporting dilemma and their implications on patient management.

Case Report
Case 1: A 3-year-old male child, with previous history of nephrotic syndrome came for follow up. The child was on treatment with steroids and was in remission. Urine analysis done, showed a spot urine protein level was 4.4g/dl and a urinary pH of 6.8. Microscopy of urine showed the presence of crystals in the shape of thorn apple (Figure 1A). Although the "thorn apple" morphology was characteristic of ammonium bi-urate crystals, the scenario of nephrotic syndrome was an unusual one. A diagnosis of ammonium biurate crystals was made. Subsequent sonographic scan of abdomen revealed stone of 1 cm in the right renal pelvis. Patient underwent extracorporeal shock wave lithotripsy for the removal of the calculi. The patient did not show any recurrence of stone in the available follow up period of 1 year.

Case 2: A 10-year-old male presented with fever and pain abdomen. Physical examination revealed icterus and tender hepatomegaly. Urine analysis showed a pH of 5.6 with microscopy of the urine showing crystals resembling round yellow spheres with radiating striations (Figure 1B). The crystals were soluble in mineral acid (Hcl) and alkali (NaOH) but insoluble in organic acid (acetic acid). Other laboratory tests showed a total bilirubin of 14 mg/dl with a direct bilirubin of 6mg/dl. Enzymes were elevated with an AST and ALT level of 3400 IU/dl and 2850 IU/dl respectively. A diagnosis of leucine crystalluria was made.

Patient was found to be Hepatitis B positive, and a clinical diagnosis of chronic liver disease was made.

Case 3: A 35-year-old female presented with generalized weakness, rash and pruritis. The patient had icterus. Blood investigations revealed a total bilirubin of 28 mg/dl and a direct bilirubin level of 22 mg/dl. Urine analysis showed a pH of 6 and clusters of fine yellow needle like crystals (Figure 1C). The crystals were identified as bilirubin crystals. Sonography of the abdomen showed carcinoma head of pancreas. The patient a partial pancreaticoduodenectomy and had an uneventful available follow up of 2 months.

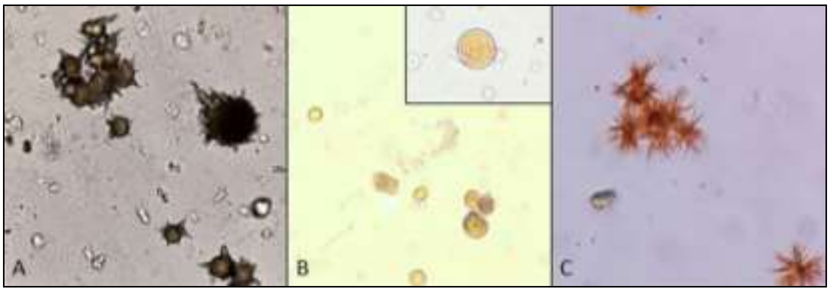

Fig 1:(A) Ammonium biurate crystals in the shape of thorn apple (200x), (B) Yellow round leucine crystals (100x) with outward striations(inset, 200X), (C) Yellow needle shaped bilirubin crystals arranged in clusters (200x).

Discussion

Crystalluria occurs due to supersaturation of solutes/metabolites derived from diseases (metabolic/inherited) or drugs. It results due to disturbance between the promoters and the inhibitors of crystallization. Promoter substances precipitate and facilitate crystal formation, e.g. calcium ions, urate, and oxalate [5]. Inhibitor substances delay crystal formation prevent adhesion to the tubular cells. Proteins like osteopontin, Tamm-Horsfall protein function as inhibitors and facilitate the elimination of crystals [6].

The biurate calculi formation occurs due to increased uric acid excretion. Tissue damage, dehydration, and infection by urease producing bacteria causes an increase in blood levels of uric acid, which when excreted in urine, increase the levels of urinary ammonium and lead to highly alkaline urine [7-9]. An highly alkaline pH, large concentrations of urate are present, while at near neutral pH, mixtures of biurate and uric acid are found, and biurate virtually disappears from the urine at a pH < 5.7, making crystallisation of biurate most probable in the near neutral pH range [10, 11]. Biurate crystals in a background of nephrotic syndrome appear to result from dehydration or long-standing urine in a 24-hour sample, however their appearance in a freshly voided sample warrants investigation for cause.

Elevated levels of bilirubin is the hallmark of poor liver function. In cases of liver disease such as cirrhosis and failure, excess bilirubin can be filtered through kidneys and precipitate forming bilirubin crystal. Bilirubin crystals are small and yellow in colour with a needle-like, granular appearance. They tend to precipitate onto other casts/cells in the urine [12]. Study by Nam *et al.* [13], showed a higher association between non-alcoholic fatty liver disease and renal stones with estimated frequency of stones 19% higher. In case 3, presence of these crystals in urine along with other serum markers were a tell-tale sign of obstructive jaundice and guided the diagnosis of the patient.

Leucine stones are usually seen in metabolic diseases which usually affect the liver [14]. Leucine crystals are yellow-brown disks with concentric rings like a tree trunk. They are seen in acidic urine and their presence points towards severe liver disease [12]. In the present case, the child with leucine crystals led to liver function tests to be done. The liver function tests showed elevated enzymes, which pointed towards an infective cause of the disease and later proved to be hepatitis.

Automated urine analysers uses electrical impedance, and image-based analysis systems, which functions by segregating particles according to particle dimensions. It scans the formed elements in urine and display the images on a screen. It requires a visual examination by a trained eye for either accepting or reclassify them before reporting the results. Automated analysers have good sensitivity in analysis of leucocytes and erythrocytes but only moderate sensitivity towards recognition of the crystals in urine. Most authors on these subjects recommend a manual examination of the specimen for crystal analysis. The pH of urine and the acid/alkali solubility in different substances can help in diagnosis of the type of crystals manually [15-17].

Conclusion

Urinary pH, concentration of the solute, presence of infections and refrigeration of sample play an important role in the formation of crystals in the urine. *In vivo* crystal formation is an indicator for tubular damage. Morphology, solubility testing with organic/mineral acids and alkali aids in diagnosis under unexpected scenarios. The reporting of these crystals with clinically relevant scenarios help to guide further patient management.

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