Cylindruria

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Abstract: The morphological analysis of urine sediment is an essential part of urinalysis and casts are important elements of urinary sediment. Their shape is typically cylindrical, with extremities often rounded. Casts form within the renal tubules and are made of Tamm-Horsfall glycoprotein (THG). Under some physiological or pathological conditions THG fibrils aggregate giving rise to casts, whose formation is favoured by a number of factors including high urine osmolality and/or low pH. Casts can be found in normal subjects, in non-renal conditions, such as fever, dehydration, and acute heart failure as well as in virtually all renal diseases. Casts can be classified on the basis of their morphology as hyaline, granular, waxy, fatty, cellular (leukocytic, erythrocytic, epithelial), containing crystals or microorganisms, pigmented and mixed. As the correct identification of casts is crucial for an accurate and timely diagnosis of renal disorders, laboratory professionals should be trained to identify and classify casts properly.

Keywords: Tamm-Horsfall glycoprotein; urinalysis; urinary casts; urinary sediment.

Introduction

Casts are important constituents of urine sediment, as they can be associated with a number of renal disorders whose diagnosis may also depends on the correct identification of urinary casts.

In this paper we describe the preanalytical and analytical factors influencing the formation and identification of casts, the mechanisms involved in cast formation, and their classification and clinical meaning. Special attention is given to granular, waxy, erythrocytic and renal tubular cell containing casts for their relevant clinical importance.

Preanalytical and analytical factors influencing the formation and identification of casts

The morphological analysis of urine sediment is an essential part of urinalysis, since it represents a crucial tool for diagnosing kidney and urinary tract disorders [1, 2]. Although many international and national guidelines provide a good support to laboratory staff for obtaining the best reliable results by using an appropriate and standardised methodology [3–5], several preanalytical issues related to collection, transportation and storage of urine samples pose serious challenges for the quality of urinalysis [6, 7]. The accurate identification and classification of urinary sediment particles including casts requires a high quality specimen, which is represented by the second void morning sample. This specimen better preserves the integrity of casts, thus limiting the chance of lysis or degeneration due to the prolonged permanence of urine in the bladder during the night rest. Midstream urine collection is another important preanalytical factor, as it ensures that the sample is free from mucus or other contaminants originating from the urethra and external areas of the urinary tract and genitals [8–10].

It is also important to inform the patient that strenuous physical exercise, such as jogging, performed in the hours preceding urine collection, may cause urinary changes including haematuria and heavy cylindruria [7].

As to the analytical phase, it is not advisable to examine strongly alkaline urine, as a high pH prevents the formation of casts and favours the lysis of other cellular elements. Additional conditions that may impair the accurate identification and classification of casts include sample contamination by genital secretions, the presence of large amounts of amorphous phosphates and crystals, as well as urine with low urinary specific gravity or low osmolality [7].
Emphasis should also be placed on procedures for sample transportation and storage. The storage of urine samples for >3 h may cause lysis and degeneration of casts and other cellular elements [11].

The quality of the analytical phase of urine sediment examination is also crucial for generating reliable data, and should entail the use of appropriate technology and instrumentation. During recent years, analytical platforms have been made available for supporting the laboratory personnel. These analysis platforms include automated urine sediment analysers based on flow cytometry, digital image capture systems or automated intelligence microscopy, even though manual microscopy with low and high magnification still remains the gold standard for this test. According to international guidelines, the use of phase contrast microscopy and polarised light is still the best approach for identification of casts and their morphological details [3, 4].

### Formation of casts

Casts are particles with a cylindrical shape with usually rounded extremities, which originate in the ascending limb of Henle’s loop, distal tubules and collecting ducts of the kidney and are made of a specific matrix, i.e. Tamm-Horsfall glycoprotein (THG) or uromodulin. This is secreted by tubular cells of the thick ascending limb of Henle’s loop and has a fibrillar structure, fibrils being unbranched and with a diameter of 9–15 nm.

Interestingly, THG is the most important constituent of the so-called physiological proteinuria, even though its role is not entirely clear (a number of potential actions have been identified, including prevention of urinary infection and urolithiasis) [12–14].

Under some circumstances, THG fibres aggregate which causes the formation of cylinders, which take the shape of tubular lumen where they are formed. The aggregation of fibres is favoured by several factors including increased intra-tubular concentration of ultrafiltered proteins, low intra-tubular pH and high osmolality, a fact that explains why casts tend to be uncommon, or in low numbers, in diluted and alkaline urine.

### Classification and clinical associations of casts

Casts have a wide spectrum of shapes, sizes and morphologies which depend on the types of particles embedded into the cast matrix. All this justifies the need for a classification of casts, which is based on both their morphology and the particles they contain (Table 1).

It is of the utmost importance to remember that since casts form in the renal tubules all elements embedded into the matrix of casts derive from the kidneys, a fact which is of considerable diagnostic importance [7].

#### Hyaline casts

These casts are composed only of THG, a fact which explains their low refractive index. Hence, their microscopic identification in bright field microscopy is challenging, and they can be more efficiently detected using phase contrast microscopy. Hyaline casts may display a spectrum of morphologies, which includes “fluffy”, compact, convoluted or wrinkled casts.

Hyaline casts can be found in normal subjects, in para-physiological conditions, such as after strenuous physical exercise, and in non-renal disorders such as fever, dehydration, acute congestive heart failure or in association with the use of Henle’s loop diuretics. However, hyaline

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
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<tbody>
<tr>
<td>Hyaline</td>
<td></td>
</tr>
<tr>
<td>Granular</td>
<td>Finely granular</td>
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<tr>
<td></td>
<td>Coarsely granular</td>
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<tr>
<td>Waxy</td>
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<tr>
<td>Fatty</td>
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<tr>
<td>Cellular</td>
<td>Leukocytic</td>
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<tr>
<td></td>
<td>Erythrocytic</td>
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<tr>
<td></td>
<td>Epithelial (containing renal tubular epithelial cells)</td>
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<tr>
<td>Pigmented</td>
<td>Haemoglobinic</td>
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<td></td>
<td>Myoglobin</td>
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<tr>
<td></td>
<td>Bilirubinic</td>
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<tr>
<td>Containing microorganisms</td>
<td>Bacterial</td>
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<tr>
<td></td>
<td>Candidal</td>
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<tr>
<td>Containing crystals</td>
<td>According to the type of crystals within the cast</td>
</tr>
<tr>
<td>Mixed</td>
<td>Hyaline-granular (the most frequent)</td>
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<tr>
<td></td>
<td>Granular-cellular</td>
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<tr>
<td></td>
<td>Granular-fatty</td>
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<tr>
<td></td>
<td>Waxy-granular</td>
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<td></td>
<td>Waxy-cellular</td>
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<td>Etc.</td>
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</table>

Some authors also include “broad casts”, which in the past were also known as “real failure casts”. These casts have an increased diameter, which is due to their formation within renal tubules which are dilated as a consequence of the chronic renal disease.
casts can also be present, in variable amounts, in all renal diseases, including glomerulonephritides, where they have been found in 100% of the patients investigated [15], and acute interstitial nephritis, in which they have been observed in 86% of cases [16]. Most importantly, whilst in the normal subjects and in the other non-renal conditions mentioned above, hyaline casts are the only urinary finding, in renal disorders hyaline casts are almost invariably associated with other types of casts and urine sediment particles [15, 16].

Granular casts

These casts have a surface composed of granules, which can vary in size (Figure 1). The granules can be rather heterogeneous, ranging from fine (finely granular cast) up to coarse (coarsely granular cast), dark, clear, and pigmented. It has been demonstrated that in patients with proteinuria, fine granules contain ultrafiltered proteins which have been reabsorbed by tubular cells [17], whilst in non-proteinuric patients coarse granules probably derive from the degeneration of cellular elements, such as leukocytes and renal epithelial cells present in the tubular lumen during cast formation [18]. The presence of granular casts always reflects renal injury, and recent studies on patients with acute kidney injury have demonstrated that they are, together with renal tubular epithelial cells (RTEC) and RTEC-containing casts, a sensitive marker of acute tubular necrosis [19–21].

Waxy casts

These casts typically display a melted wax (waxy) appearance (Figure 2), which confers them a high refractive index. They are frequently dark, with blunt extremities, indented and cracked edges and a large size, which is often several times that of other types of casts.

Interestingly, their composition remains poorly understood. In one recent prospective study on waxy casts in patients with glomerulonephritis it has been reported that THG is not found in these casts [22], a fact which, however, would need confirmation by others studies and further investigation.

Also the clinical associations of waxy casts are poorly known, because those reported in atlases and textbooks (e.g. renal function impairment either acute or chronic, renal amyloidosis, etc.) do not have any sound support from literature. To date, the only sound investigation on waxy casts is the prospective study mentioned above [22], in which the urine sediment of 287 patients with different types of glomerulonephritis was evaluated in a standardised way by phase contrast microscopy. Waxy casts were found in only 29 patients (13.6%), a frequency which was much lower than that of all the other types of casts. A statistically high frequency of waxy casts was found in acute post-infectious glomerulonephritis and in renal amyloidosis (44.5% for either condition), whilst it was low in idiopathic membranous nephropathy (6.0%) and nil in focal and segmental glomerulosclerosis. Patients with waxy casts, compared with those without, had
significantly higher levels of serum creatinine (159 vs. 97 μmol/L, p<0.0001) and the presence of waxy casts correlated significantly with granular casts and leukocytic casts, whilst there was no association with hyaline casts.

**Fatty casts**

These casts may contain lipid droplets, oval fat bodies or cholesterol crystals, and are often associated with the free forms of these elements. Their identification may require the use of polarised light microscopy, under which fatty particles embedded into the cast matrix appear as “Maltese crosses”. The presence of fatty casts in urine is associated with heavy proteinuria as it is found in patients with nephrotic syndrome.

**Cellular casts**

These casts include all cylinders containing any type of cells which may be present in renal tubules such as leukocytes, erythrocytes and RTEC. Therefore, the classification of cellular casts encompasses leukocytic, erythrocytic, and RTEC casts.

*Leukocytic casts* contain different amounts of leukocytes which at times, due to particular physico-chemical features of the urine, can hardly be distinguished from RTEC. Also in such cases the use of phase contrast microscopy can facilitate the correct identification of the particles.

In patients with urinary tract infection, the finding of leukocyte casts suggests the involvement of the renal parenchyma, a fact which is important from the clinical standpoint. It is a common view that leukocyte casts are found in patients with acute interstitial nephritis [22, 23], whilst it is less known that they can also be found in patients with glomerular diseases [15].

*Erythrocytic casts* may contain different amounts of red blood cells (Figure 3). In some cases the number of erythrocytes is high and the presence of the matrix can be no longer distinguished.

The presence of erythrocyte casts is considered a marker of glomerular hematuria, especially when they are associated with free dysmorphic erythrocytes in the urine. Erythrocyte casts are found in most glomerular diseases, especially in those with glomerular cell proliferation (the so-called proliferative glomerulonephritides) [15], although their frequency is highly variable among studies [7]. However, in contrast with the current view, erythrocyte casts can also be found in patients with acute interstitial nephritis (AIN), as it has been shown in a recent retrospective study on 21 patients with AIN due to different causes, six of whom had erythrocytic cylindruria (28.5%). It is hypothesised that in such cases the formation of erythrocyte casts might be the consequence of interstitial vessels injury secondary to interstitial cell inflammation, with extravasation of erythrocytes into the interstitial space and subsequent passage within the tubular lumens through tubular basement membranes breaks, which in AIN are very common [16].

*Renal tubular epithelial cells casts* (epithelial casts) may contain various amounts of tubular cells (Figure 4), and are often accompanied by free renal tubular cells, which ultimately help identifying this type of cast. Some challenges may emerge in their accurate identification, especially when the cells are degenerated and are hardly distinguishable from leucocytes. For such cases phase contrast microscope or supravital stains are recommended.

The epithelial casts can be found in a number of renal diseases including glomerulonephritis [15] and acute interstitial nephritis [16]. In a pilot study published a few years ago [19], it was demonstrated that a cast scoring index (CSI) based on the combined amount of RTEC casts and granular casts in patients with acute kidney injury correlated with the renal outcome, the CSI being significantly higher in patients who did not recover renal function.

Figure 3: An erythrocyte cast with packed erythrocytes (phase contrast microscope, original magnification 400×). By courtesy of Dr. G.B. Fogazzi.
Myoglobin casts have a reddish brown colour but are usually not associated with red blood cells or erythrocyte casts. They can be observed in the urine of patients with acute kidney injury associated with severe muscle damage leading to rhabdomyolysis.

Bilirubin casts typically display the yellow-brown hue of bilirubin. They can be observed in patients with liver disease and/or conditions characterised by bilirubinuria [7].

Mixed casts. A large variety of mixed casts can be found in the urine, some of which are listed in Table 1. Among them hyaline-granular casts are by far the commonest. In fact, they have been found in 100% of 100 patients with different types of glomerulonephrits [15] and in 17 out 21 patients with AIN due to different causes (81%) [16].

Casts containing crystals or microorganisms

Virtually any type of crystals may be found in casts, those made of calcium oxalate, either mono- or bihydrated, being the commonest ones.

These casts clearly indicate that crystals have precipitated within the tubular lumen, a finding which may be useful in the diagnosis of crystalluric forms of acute kidney injury, such as acute urate nephropathy.

Casts containing microorganisms can be caused by infections of renal tissue. Bacterial casts can be difficult to identify and can be distinguished from other types of casts using phase contrast microscopy.

The presence of casts containing Candida is suggestive for a systemic candidiasis with visceral involvement [7].

Pigmented casts

Pigmented casts have peculiar colour which reveals the presence of pigments derived from the breakdown of cells or pigmented molecules.

Haemoglobin casts originate from erythrocytes, have a typical hue that varies between brown and red, and have often a granular aspect. They are usually found in association with free red blood cells and erythrocyte casts in patients with renal bleeding from various causes. In rare instances haemoglobin casts are due to haemoglobinuria as it may occur in disorders associated with intravascular haemolysis.

Conclusions

The casts are considered one the effective urinary sediment markers for diagnosing kidney disorders. The origin, composition, morphology and clinical associations have been clearly defined for many of them, whereas less information is available for others (i.e. waxy casts). Some interesting findings have emerged from recent studies, especially on the value of granular and RTEC casts in identifying patients with acute kidney injury associated with acute tubular necrosis, the possible presence of erythrocyte casts in patients with AIN and the frequency and clinical associations of waxy casts in patients with glomerulonephritis.

The scientific development in the investigation of urine corpuscular elements over the past 10 years have been mainly driven by the commercialisation of automated analysers using different technologies, such as automated microscopy in bright field, flow cytometry and digital image capture systems. The use of these tools is highly recommended for the standardisation, accuracy and efficiency of urinalysis. However, the overall accuracy of these instruments in identifying casts does need further development, and for the time being the best identification of cast still rests on traditional morphological analysis.

As the identification of casts is crucial for the accurate and timely diagnosis of renal disorders, laboratory professionals should be educated to accurately recognise and classify casts during analysis of urine sediment. The laboratory staff should also be specifically trained in the use of the standard methodology for identification and classification of casts, including bright field, phase contrast or
polarised light microscopy, as well as to the use of specific cytological staining. Therefore, it is essential that clinical laboratories should be involved in reliable internal quality control (IQC) programs and external quality assessment (EQA) schemes for both the preanalytical and analytical phase of urinalysis [24–26]. The laboratories should be directly connected with international and national societies or working groups such as the European Federation of Laboratory Medicine (EFLM) or the Italian intersocietary SIBioC/SIMEl working group for urinalysis or Italian urinalysis working group (GIAU) [27]. The members of these groups promote scientific updates, multicenter studies, meetings, conferences and other educational activities on urinalysis. Our ultimate goal is to enhance competency in morphological and clinical analysis of corpuscular elements in urine to produce updated, efficient, and straightforward laboratory reports in connection with the clinical needs of the patient according to the modern concept of personalised medicine [28].

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