Occult Hematuria Detected on Health Screening

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Abstract: The detection rate of occult hematuria found on health screening is considerably high, ranging from 2.8% to 16%, which is double or triple that of proteinuria. Diseases in adults that cause hematuria can be broadly divided into three groups: systemic disease involving the kidney, renal parenchymal disease, and urologic disease. Systemic diseases causing damage to the kidney include hypertension, diabetes mellitus, and many other diseases. Important renal parenchymal diseases are glomerulonephritis and its related diseases. When systemic diseases and renal parenchymal diseases are excluded, there is a high possibility of urologic diseases such as malignant tumor, urolithiasis, and urinary tract infection. In children, it is also necessary to consider both pediatric and urologic diseases. In particular, hereditary nephritis and congenital urinary tract malformation are clinically important. Occult hematuria, which is frequently found on health screenings, has various possible causes. In approximately 80% of the cases detected, however, the cause was not discovered and a positive diagnosis was not possible. Therefore, it is important to develop effective strategies for diagnosing the cause of microscopic hematuria.

Key words: Occult hematuria; Mass screening

Introduction

Hematuria is defined by the presence of red blood cells (RBCs) in urine. RBCs in urine are generally regarded as pathologic when 3–5 or more per field are found by microscopic observation of urinary sediment under high (400-fold) magnification. Hematuria is classified as macroscopic (visible to the naked eye) or microscopic (recognized only under a microscope), or by the presence/absence of concomitant symptoms as symptomatic or asymptomatic.
Occult hematuria found on mass screening is asymptomatic and microscopic in most cases, and accounts for 2.8–16% of subjects. Systemic disease, renal parenchymal disease, and urologic disease are the main causes of this condition. In spite of close examination, the etiology remains unclear in about 80% of cases, indicating the difficulty in determining the cause of occult hematuria.

This paper reviews diseases that may cause clinically relevant occult hematuria detected on mass screening and discusses how to examine and treat it in adults. Occult hematuria in children is also outlined briefly.

### Occult Hematuria in Mass Screening

Hematuria is found frequently among mass screening subjects, with the reported incidence ranging from 2.8% to 16%. Although the frequency varies according to the target of screening, the detection rate is usually double or triple that of proteinuria. The percentage of subjects positive for occult hematuria generally increases with age. The rate is higher in women, and that may be explained by the higher incidence of urinary tract infection and contamination by menstrual blood.

The diseases causing microscopic hematuria and their frequencies as reported in the literatures are listed in Table 1. Among the various causes of microscopic hematuria, systemic diseases such as diabetes mellitus and hypertension, which cause damage to the kidney, account for 7.3–11%. Glomerulonephritis, a clinically significant disease related to abnormal urine test results, is found in 2.1–9% of subjects. Urologic tumor is found in 0.4–3.8% of subjects. Although its frequency is relatively low, this disease is life-threatening and therefore clinically significant. When the subject is 40 years old or older, the presence of hematuria, even if it is microscopic, warrants consultation with a urologist. Urolithiasis is diagnosed in 2.5–7.9% of subjects, and urinary tract infection in 0.5–18% of subjects. Both conditions are relatively common and should be kept in mind when occult hematuria has been found on health screening.

Guidelines have not been established for the follow-up observation of patients with asymptomatic hematuria. It is, however, important that any condition likely to lead to renal failure should not be overlooked. Based on their long-term observation of subjects with abnormal urine test results, Yamagata et al. reported that about 50% of subjects positive for hematuria alone experienced disappearance of hematuria, about 40% showed no change, and about 10% eventually developed proteinuria and were diagnosed as having chronic nephritis. In addition, they reported that 75% of subjects who were positive for proteinuria with or without hematuria were later diagnosed as having chronic nephritis. Subjects positive for hematuria alone showed very little worsening of
Diseases That May Cause Hematuria

Diseases that may cause hematuria are broadly divided into three groups: systemic disease, renal parenchymal disease, and urologic disease.

1. Systemic disease

Systemic diseases that may cause hematuria and proteinuria and lead to renal failure include hypertension, necrotizing angiitis, diabetes mellitus, hyperuricemia, amyloidosis, sarcoidosis, collagen diseases such as systemic lupus erythematosus (SLE), multiple myeloma, leukemia, Goodpasture’s syndrome etc. (Table 2). Diseases showing hemorrhagic diathesis, such as hemophilia and thrombocytopenic purpura, while not causing renal disorders, can be the cause of hematuria. In general, these diseases are seldom detected by occult hematuria on health screening, but they are often found as a result of other signs and symptoms or laboratory findings. Nevertheless, it should be noted that while many diseases can cause microscopic hematuria, it is difficult to diagnose any of them positively as the cause. They should be regarded as probable diagnoses after other possible causative diseases have been excluded.

Table 2 Systemic Diseases That May Cause Hematuria

<table>
<thead>
<tr>
<th>Disease</th>
<th>Syndrome</th>
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</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Necrotizing angiitis</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Hemophilia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenic purpura</td>
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</tbody>
</table>

Renal function, whereas 10% of subjects positive for proteinuria and 30% of those positive for both hematuria and proteinuria developed increased creatinine levels within 10 years. Thus, when hematuria alone is positive, the probability is low that it will develop into a serious disease in the future. Therefore, we consider it sufficient to follow the course of the condition through non-invasive tests, such as urinalysis, blood examination, and ultrasonography.

**Diagnostic Procedures for Hematuria**

Urinalysis performed as part of a health screening usually employs a paper strip test. Therefore, when the test has indicated hematuria, it is necessary to carry out microscopic observation of urinary sediments to determine the severity of hematuria. It is also important to look for irregularities in the size and shape of RBCs, and the presence of white blood cells and casts in urine. In addition, the following examinations should be performed: a general physical examination; blood pressure measurement; complete blood count; blood biochemical tests for BUN, creatinine, and serum electrolytes; serological assays of ASLO, immunoglobulins, and complement; urinary cytology, and ultrasonography of the kidney and urinary tract.

In general, the possibility of renal parenchymal disease is high when the following are noted: proteinuria, urinary casts, edema in the lower limbs and face, hypertension, renal dysfunction, elevated levels of ASLO and IgA, decreased complement, and bilateral renal atrophy. Subjects who have clinical signs and laboratory findings suggesting the presence of renal parenchymal disease should be referred for detailed examination by a nephrologist. The final diagnosis should be made by renal biopsy.

When such abnormalities are not found, when urinary cytology shows positive results, or when ultrasonography suggests urologic disease, urologic examinations such as drip infusion pyelography (DIP), cystoscopy, CT, and MRI should be performed.
ated with persistent hematuria and proteinuria without renal dysfunction. From the viewpoint of treatment, it is critical that these two conditions be differentiated (Table 3). Glomerulonephritis is highly likely when RBCs in urine are irregular in size or shape, when hematuria is accompanied with proteinuria or urinary casts, when there is hypertension or accompanying edema in the lower limbs, when blood test reveals renal dysfunction, or when there is elevated ASLO or IgA or decreased complement. It is also necessary to consider hereditary nephrites such as Alport’s syndrome, in which nephritis is accompanied with impaired hearing, and thin basement membrane disease, in which benign recurrent hematuria is present. These diseases are more likely to show the presence of a family history (Table 3). The definitive diagnoses of these conditions are established by histopathological determination of the glomerular abnormalities, and treatment modalities are then determined. Therefore, when these diseases are suspected, it is necessary to refer the subject to a nephrologist.

3. Urologic disease

Urologic diseases are highly likely to be involved when the above-mentioned systemic diseases and renal parenchymal diseases are excluded, necessitating close examination by urologists.

The most important urologic diseases detected by hematuria are malignant tumors such as renal cell carcinoma, renal pelvic and ureteral cancer, and bladder cancer often manifest with macroscopic hematuria as the initial sign. Although it is uncommon to find these diseases through close examination of microscopic hematuria, it is important not to overlook them because they are life threatening.

If the urinary cytology and DIP, which are useful tests for renal pelvic and ureteral cancer, indicate the possibility of cancer, further examination by CT, retrograde pyelography, or ureteroscopy should be performed to establish the diagnosis. Bladder cancer is the most frequent disease in the field of urology. Both the urinary cytology and cystoscopy are useful for diagnosing this disease. Almost all cases of bladder cancer can be diagnosed by cystoscopy. Renal cell carcinoma is usually detectable by ultrasonography when the tumor measures 3 cm or more in diameter. Definitive diagnosis is obtained by CT or MRI. Hematuria rarely serves as a clue to the presence of prostate cancer, whose major symptoms are dysuria, pollakisuria, sense of residual urine etc. This disease, however, should also be considered as the cause of hematuria.

Another important disease entity is urolithiasis, which are classified into renal stones, ureteral stones, and bladder stones, according to their site. Although renal and ureteral stones are commonly accompanied with severe back pain or flank pain, it is not uncommon for these conditions to be detected by examination on occult hematuria. Urolithiasis occur more frequently than malignant tumors and more often cause microscopic hematuria, thus requiring attention. Ultrasonography, DIP, or CT is required to establish the diagnosis.

Urinary tract infection is also a frequent cause of hematuria. Since white blood cells and bacteria are found in the urine, it is not difficult to make this diagnosis. Appropriate antibiotic therapy based on the results of bacterial culture of the urine should be given to the patient. In general, pyelonephritis is accompanied with fever and back pain, and cystitis is accompa-
nied with micturition pain, pollakisuria, and cloudy urine. However, when there are few symptoms, chronic urinary tract infection should be suspected. In such cases, urolithiasis, hydronephrosis, vesicoureteral reflux, prostate hypertrophy, or neurogenic bladder may be an underlying condition, and close examination of the urinary tract is required. If asymptomatic microscopic hematuria and pyuria are persistent, renal and urinary tract tuberculosis is a possibility that should not be overlooked (Table 4).

In addition to the above diseases, a variety of diseases of the kidney and urinary tract can cause hematuria. These include renal cyst, polycystic kidney, horseshoe kidney, atrophic kidney, idiopathic renal bleeding, hydronephrosis, double renal pelvis and ureter, ureteral stenosis, vesicoureteral reflux, vesical diverticulum, interstitial cystitis, radiation cystitis, bladder neck contracture, prostatic hypertrophy, prostatitis, prostatic stones, urethral stricture, and urethral caruncle etc. It is therefore important to refer to urologists for closer examination.\textsuperscript{10,11}

**Occult Hematuria in Children**

When examining children, it is necessary to consider both urologic and pediatric diseases. For health screening of school children in Japan, the Tokyo system has been widely adopted, by which children with abnormal results on a primary urine test are subjected to a secondary urine test, and those with abnormal results on the secondary test are subjected to a tertiary examination consisting of urinalysis including urinary sediment, medical examination by a physician, measurement of blood pressure, and blood test. The follow-up plan and the management of daily activities are clarified to a greater extent than in adults.\textsuperscript{1,3}

The positivity rate for occult hematuria on primary urinary screening was reported to be 1.9% among 4,930,000 elementary school children and 5.1% among 2,420,000 junior high school students. The corresponding rates on secondary screening are 0.5% among 120,000 elementary school children and 0.9% among 170,000 junior high school students. These percentages are two- to threefold higher than those for proteinuria.\textsuperscript{12} As a result of tertiary screening of those positive for occult hematuria together with those positive for proteinuria, nephritis was found in 1.0% and urinary tract infection in 2% of 12,140 elementary school children, while nephritis was found in 0.8% and urinary tract infection in 1.8% of 10,145 junior high school students.\textsuperscript{12}

Although few detailed reports exist on the causes of microscopic hematuria in children, urinary tract infection, hydronephrosis, vesicoureteral reflux, urinary tract stones, and nephritis have been detected as causes (Table 5).\textsuperscript{1,13}

Among children with abnormal urine test results, including proteinuria on health screening in schools, the frequency of glomerulonephritis is high, and hereditary nephrites such as Alport’s syndrome and thin basement membrane disease are also important causative conditions. Among renal disorders associated with systemic diseases, nephritis due to purpura, nephritis due to SLE, and Goodpasture’s syndrome are important. Hemorrhagic diseases such as hemophilia and thrombocytopenic purpura can also cause hematuria. Urinary tract infection and urolithiasis may also be detected through occult hematuria.

In addition, children may present congenital renal and urinary tract diseases including poly-

**Table 4** Urologic Diseases That Cause Hematuria

<table>
<thead>
<tr>
<th>1. Malignant tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma, Renal pelvic and ureteral cancer, Bladder cancer, Prostate cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Urolithiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney stones, Ureteral stones, Bladder stones</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis, Cystitis, Renal and urinary tract tuberculosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Others</th>
</tr>
</thead>
</table>

**Secondary**

\textsuperscript{10,11}
cystic kidney, congenital hydronephrosis, and vesicoureteral reflux. Congenital hydronephrosis and vesicoureteral reflux can be detected by abnormal urine test results including hematuria, although pyelonephritis is a more common clue to find them. Therefore, it is necessary to perform diagnostic imaging procedures such as ultrasonography, intravenous pyelography, and cystography in cooperation with pediatricians and urologists (Table 6). 1,14) No imaging techniques are employed by the Tokyo system even for tertiary screening; this should be reconsidered in the future. 1)

However, if hematuria is the only abnormality found in health screening in school, the probability of detecting serious diseases that require treatment or close follow-up is as low as 5%, 1) suggesting that the clinical significance of microscopic hematuria is low in children as well as in adults. Thus, follow-up observation generally seems to be sufficient for positive examinees, with no need for renal biopsy or strict control of daily activities including limitations on diet and exercise.

**Conclusion**

Occult hematuria found on health screening has been outlined, with most attention focused on adult cases. Although the detection of hematuria on health screenings is frequent, it rarely leads to diagnosis of the causative disease. It is important to establish effective measures for diagnosing the cause of occult hematuria and to provide useful methods of follow-up observation.

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**REFERENCES**

7) Hattori, R., Kinukawa, T., Matsuura, O. et al.: Clinical features of asymptomatic microhema-

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**Table 5 Diseases That Cause Microscopic Hematuria in Children**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Urinary tract infection</th>
<th>Hydronephrosis</th>
<th>Vesicoureteral reflux</th>
<th>Urolithiasis</th>
<th>Nephritis</th>
<th>Polycystic kidney</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murakami et al.</td>
<td>0 (0)</td>
<td>3 (1.1)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>6 (2.2)</td>
<td>1 (0.4)</td>
<td>264</td>
<td>275</td>
</tr>
<tr>
<td>Kawamura et al.</td>
<td>13 (12)</td>
<td>8 (7.5)</td>
<td>4 (3.8)</td>
<td>3 (2.8)</td>
<td>2 (1.9)</td>
<td>0 (0)</td>
<td>76</td>
<td>106</td>
</tr>
</tbody>
</table>

**Table 6 Pediatric Diseases That Cause Hematuria**

1. Primary glomerulonephritis
2. Hereditary nephritis
   - Alport’s syndrome, Thin basement membrane diseases
3. Systemic disease
4. Urinary tract infection
   - Pyelonephritis, Cystitis
5. Congenital anomaly
   - Polycystic kidney, Congenital hydronephrosis, Vesicoureteral reflux


