THE CLINICAL SIGNIFICANCE OF HEMATURIA

With Illustrative Case Reports

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Hematuria, or the presence of blood in the urine, should not be considered as a clinical entity for which treatment is instituted, but rather as a symptom which requires immediate investigation to ascertain the underlying, responsible, etiologic factors.

As a general rule, the presence of blood in the urine alarms the patient sufficiently that he seeks medical advice and relief. However, it is unfortunate that, in many instances, the hematuria is intermittent in character and, when the bleeding subsides, a false sense of security is established. The patient presumes that he is well and, as his general health may not seem to be impaired, he appears justified in such deductions. But to the physician, the cessation of bleeding is no indication that its significance can be minimized or its importance lessened and a delay in complete urological investigation should not be countenanced.

Herman[1] of Philadelphia, in a study of 150 cases of diseases of the kidney, noticed the presence of hematuria in 43.3 per cent of this group. It is estimated that in 54 per cent of renal tumors in adults, the initial symptom is hematuria.

In a recent survey of cases of tumor of the bladder collected by the Carcinoma Registry of the American Urological Association[2], hematuria was the cardinal symptom in 826 of the 902 cases in the Registry, and it was the initial symptom in 573 or 69.37 per cent of the 826 patients who complained of bleeding.

In a series of 798 consecutive cases of hematuria reviewed at the Cleveland Clinic a few years ago[3], the bleeding was due to a new growth in the genito-urinary tract in 32 per cent; in 11 per cent it was associated with renal tuberculosis; and in 16 per cent, calculi were the responsible factors.

Kretschmer[4] reviewed 860 cases of hematuria and noted that in 235 or 76.5 per cent of 307 cases in which the hematuria was associated with a lesion in the bladder, the etiological factor was either a papilloma or a carcinoma. Of 307 cases of lesions of the bladder associated with this symptom, tumor was the inciting cause of hemorrhage in 235 cases (76.5 per cent); stone ranked second and tuberculosis third. In 96 per cent of the 860 cases, the hematuria was associated with lesions within the genito-urinary tract. In nine cases, the blood in the urine was due to general disease, while in 12 cases the cause of bleeding was not determined.

In 1,500 admissions to the urological service at the Brooklyn Hospital, Rathbun[5] found hematuria to be the outstanding symptom in 203 or 13.5 per cent of the cases. He stated that in many instances this was the only symptom mentioned by the patient, while in a second group the only complaint was of red blood cells in the urine. In 106 of 203 cases, or more than 50 per cent, a neoplasm was found in the genito-urinary tract. Dr. Rathbun stated, "If we could impress upon every man practicing medicine the fact that in 50 per cent of all cases, hematuria is produced by a tumor and that a large majority of these cases are malignant or potentially malignant, we would do more to reduce our cancer mortality and morbidity than can possibly be done in any other way."

Eight malignant tumors of the kidney occurred in Rathbun's series and in 7, or 87 per cent, bleeding was the prominent symptom. There were 81 cases of carcinoma of the bladder and, in this group, bleeding occurred in 61, or 75 per cent. Sixty-one patients with carcinoma of the prostate were included in the report. Here again, bleeding was prominent in 7 or 11.4 per cent. Bleeding occurred in 22 or 66.6 per cent of 33 patients with papilloma of the bladder. In a series of 274 cases of hypertrophy of the prostate, bleeding occurred in 17 or 6.1 per cent.

MacKenzie[6] in 1932 studied 2,240 cases of gross hematuria, the patients having been admitted to the Department of Urology at the Royal Victoria Hospital from 1928 to 1932. He found the following sources of bleeding: kidney, 41.38 per cent; ureter, 12.23 per cent; bladder, 20.80 per cent; prostate, 17.90 per cent; urethra, 5.53 per cent; and unclassified, 2.14 per cent. He concluded: "In plain terms, of the 2,240 cases treated, approximately 75 per cent were due to these grave conditions. Surely this cannot fail to impress us with the fact that red blood cells have no place in the normal urine, and that they are caused by some pathological condition which it is our duty to discover."

The significance of the detection, on microscopic examination, of blood in the urine likewise must not be passed over lightly, and careful examinations to determine the cause should be employed in this group of cases. If, during the course of examination, the presence of red blood cells is detected in the urine and if symptoms referable to the genito-urinary tract are present, complete urological investigation is advisable. If, however, there are no symptoms referable to the genito-urinary tract, microscopic examination may be repeated at short intervals of time. Again, if red cells are constantly present or if they are found intermittently, complete investigation of the genito-urinary tract is essential. In women, a specimen of urine secured by catheterization obviously should be studied.

Patients with hematuria may be divided into three distinct groups:

1. *Hematuria Associated with Systemic Diseases and General Conditions.*

A. Blood dyscrasias:
   1. Hemophilia
   2. Polycythemia vera
   3. Purpura hemorrhagica
   4. Leukemia

B. Following acute infections:
   1. Scarlet fever
   2. Tonsillitis
   3. Measles
   4. Small pox

C. Deficiency and dietary disease:
   1. Scurvy
   2. High protein diet

D. Following medication
   1. Urotropin
   2. Cantharides
   3. Turpentine
   4. Sodium salicylate
   5. Mandelic acid

E. Miscellaneous
   1. Hodgkin's disease
   2. Hypertension with nephritis

II. *Hematuria Associated with Extra-Urinary Pathology:*

A. Diverticulitis of colon
B. Carcinoma of rectum
C. Appendicitis
D. Inflammatory disease of the pelvis

III. *Intrinsic Lesions Within the Genito-Urinary Tract:*

A. Kidney
   1. Infection
   2. Tumor
   3. Polycystic kidney
   4. Tuberculosis
   5. Calculi
   6. Nephritis

B. Ureter
   1. Tumor
   2. Stone
   3. Stricture

C. Bladder
   1. Tumor
   2. Inflammation
   3. Calculi
   4. Foreign bodies
   5. Ulcer

D. Bladder neck
   1. Prostate, including seminal vesicles
E. Urethra
   1. Infection
   2. Stricture
   3. Foreign body
   4. Tumor
   5. Following instrumentation
   6. Ulcer

While this classification does not include every lesion or condition which may be conducive to the presence of blood in the urine, it serves to indicate the intensive investigation which is necessary if a correct diagnosis is to be established.

In some instances, the history elicited from the patient is of value in determining the proper approach to the problem, although, as will be observed from some of the cases reported, it may be misleading. Similarly, the presence of two coexisting pathological conditions must not be overlooked.

If, following endoscopy, cystoscopy, and the employment of pyelograms, a responsible lesion is not found, complete medical examination and intensive employment of laboratory procedures are necessary. This is well emphasized by the findings of Locke and Minot[7] who observed hematuria in 15 per cent of 110 cases of chronic myelogenous leukemia. These writers also stated that 20 per cent of their patients with hemophilia complained of hematuria and added that this symptom might be the only local manifestation of underlying disease.

Squier and Newburgh[8] found red cells in the urine after the patient had followed a diet high in proteins, thus emphasizing the rôle diet may play in the production of hematuria.

The relationship between deficiency of vitamin C (scurvy) and hematuria, as Stepp[9] and Engelkes[10] have emphasized in their reports, has stimulated further study in this field, and other writers have reported similar cases.

Thus, determination of the cause of hematuria requires an accurate history and complete physical examination supplemented by such essential laboratory procedures as tests of urinary function, urinalysis, complete study of the blood including bleeding and clotting time, and other procedures as deemed advisable.

Complete study of the urinary tract is essential, and this should include endoscopic and cystoscopic examinations, examination of specimens of urine from the kidneys, tests of function, and pyelography. If these procedures are employed, I believe that, in the vast majority of cases, an accurate diagnosis can be established and therapy instituted early in the course of the disease.

The following brief case histories illustrate conditions which may be associated with hematuria and emphasize the futility of attempting to establish a diagnosis from the standpoint of the history elicited from the patient.

Case Reports

Case 1: A man, 51 years of age, entered the Clinic on April 8, 1937, complaining of recurrent red spots on the skin, bleeding from the tongue and rectum, and blood in the urine. Prior to admission, he had always been in good health. In the preceding year, small red spots had appeared on his trunk and extremities on several occasions. During the last few attacks, blood had been noted in the urine and occasionally the urine was quite red. Bleeding from the rectum had also occurred.

General examination gave essentially normal findings except for small petechial hemorrhages on the extremities and mucous membranes of the mouth. The spleen was not enlarged and there was no adenopathy. The tourniquet test brought out petechiae.

Blood studies: The red blood cells numbered 3,580,000. There were moderate anisocytosis and poikilocytosis and pallor. Examination gave the following findings: reticulocytes, 1.8 per cent; volume of packed red blood cells, 73 per cent of normal (33 cc. per 100 cc.); volume index, 1.01; hemoglobin, 65 per cent of normal (110 gm. per 100 cc. with Haden Hauser hemoglobinometer); color index, 0.90; saturation index, 0.89; white blood cells, 3,300 per c.mm.; differential count: neutrophils, 51 per cent; lymphocytes, 43 per cent; monocytes, 6 per cent; icterus index, 5; platelets, 50,000 per c.mm.; bleeding time 5 minutes; clot retraction—none; nothing abnormal in concentrated preparation of the white blood cells.

Comment: In this case, the hematuria was definitely associated with the blood dyscrasia.

Final diagnosis: Essential thrombopenia (purpura).

Case 2: The patient was a man, 57 years of age, who entered the Clinic on February 3, 1937, complaining of blood in the urine. The first attack of hematuria occurred in 1914, lasted two to three months, and then subsided spontaneously. The next attack occurred in 1928 and lasted 3 to 4 months, during which time the kidney pelves were washed out with a solution of silver nitrate. In 1935, blood was again noticed in the urine and this time it was present for about 3 months. At the time of our examination, blood had been present in the urine for 6 months, but was not associated with other urinary symptoms. The diet had always been inadequate in fruit and vegetables.

General examination revealed no abnormalities. Examination of the blood showed it to be normal. The urine contained numerous red blood cells.

Cystoscopic examination revealed no abnormalities. Numerous red blood cells were found in a specimen of urine from the kidneys. The tests of renal function showed normal elimination.

A diagnosis of scurvy was made.

In addition to increasing the amount of fruit in the diet, two tablets of cevitamic acid, 10 mg. were prescribed after meals, and a course of moccasin venom in initial doses of 0.4 cc. was also given. This treatment was followed by striking results.

Comment: In this case, aside from red blood cells in the specimens of urine from the kidneys, the urological examination gave normal findings. Complete studies of the blood failed to show any blood dyscrasia. A final diagnosis of scurvy was made, and the symptoms disappeared following dietary adjustment, cevitamic acid, and moccasin venom therapy.

Final diagnosis: Scurvy.

Case 3: A man, 32 years of age, was seen in consultation on April 8, 1937. His complaint was of blood in the urine. For six weeks he had been in the hospital where treatment had been given for pus in the urine, enormous doses of urotropin having been administered over a period of three weeks. During the ten days preceding our examination, hematuria had been quite profuse and the patient complained of extreme irritability of the bladder.

Cystoscopic examination revealed a pronounced chemical cystitis. Pyelograms showed normal findings as did cultures of the urine.

Comment: In this case an acute chemical cystitis had been induced by the large doses of urotropin. The bleeding subsided by forcing fluids and the administration of sodium bicarbonate. Urological examination 2 months later revealed no abnormal findings.

Final diagnosis: Chemical cystitis.

Case 4: A man, 40 years of age, entered the Clinic on October 26, 1937, complaining of hematuria and aching type of pain in the region of the left kidney. Three years previously, the patient had passed three stones and hematuria had been noted at that time. Seven weeks preceding our examination, blood again appeared in the urine and the aching type of pain in his back had been present for a few days. No other urinary symptoms were noticed and a roentgenogram taken previously showed no evidence of renal calculi.

A pyelogram taken in the Clinic showed a nonopaque stone in the pelvis of the kidney.

Comment: In this case, the bleeding preceded pain in the back and a roentgenogram did not show the stone in the pelvis which was not demonstrable until the pyelogram was made.

Final diagnosis: Nonopaque stone in the pelvis of the left kidney.

Case 5: A woman, 29 years of age, entered the hospital on February 17, 1930. Her complaint was of blood in the urine. This had first been observed two years previously, but had not been accompanied by any other urinary disturbances at that time. The bleeding continued for one month and then subsided. One year later, blood was again noted in the urine, and it persisted for 2 months. Bleeding had been present for 3 weeks preceding our examination but was the only complaint.

Urological investigation established the diagnosis of tuberculosis of the left kidney and a nephrectomy was performed.

Comment: In this instance, although the history of intermittent hematuria dated back over a period of two years, there were no other urinary symptoms. Following nephrectomy, the patient has remained free from symptoms.

Final diagnosis: Tuberculosis of the left kidney.

Case 6: A woman, 57 years of age, entered the Clinic on April 30, 1934, complaining of blood in the urine and high blood pressure. The blood in the urine had first been noticed two years previously, and had lasted for only one day. One year later, blood was again present in the urine but no other urinary

symptoms occurred. Medicine was prescribed at this time and in two weeks the bleeding subsided. One week preceding our examination, blood again was present in the urine, casts were found in the urine, and a diagnosis of nephritis was made. At this time the patient entered the Clinic for examination.

Cystoscopic examination revealed a large, papillomatous growth in the region of the left ureteral orifice. This was fulgurated and radium implanted at the base of the tumor. A pathological diagnosis of papilloma of the bladder was made. A recurrence developed one year later and fulguration was again employed, since which time cystoscopic study has revealed no evidence of a recurrence.

Comment: In this case, bleeding had occurred 2 years previous to examination and, due to the associated high blood pressure and casts in the urine, a diagnosis of nephritis had been made. When, however, cystoscopic examination was employed, the correct diagnosis of a papilloma of the bladder in addition to hypertension and nephritis was established.

Final diagnosis: Hypertension, nephritis, papilloma of the bladder.

Case 7: A girl, 20 years of age, entered the Clinic on February 2, 1937, complaining of blood in the urine. Aside from appendicitis 2 years previously, for which an appendectomy had been performed, the patient had been in good health. Albuminuria had been noted for 10 years. For 6 months, she had been aware of the presence of blood in the urine, believing it to be due to kidney disease. She had nocturia once, and occasional frequency. Only a slight amount of blood appeared in the urine and at times she was free from it for weeks.

Cystoscopic examination revealed a large tumor on the left lateral wall of the bladder. Resection of the bladder was performed February 18, 1937.

Pathological diagnosis: Lymphosarcoma of the bladder.

Comment: In view of the presence for years of albumin in the urine and only a slight amount of blood in the urine, a diagnosis of nephritis had been made previously. Cystoscopic examination, however, revealed the presence of a tumor of the bladder.

Final diagnosis: Lymphosarcoma of the bladder.

Case 8: A man, 62 years of age, entered the Clinic on March 6, 1935, complaining of frequency of urination, slight difficulty in voiding, and blood in the urine. Two years previously, some difficulty in voiding and hematuria had been noted. Since that time, there had been nocturia two or three times, but occasionally the urine was clear. Two days before examination, complete retention developed.

Examination of the rectum revealed enlargement of the prostate, grade II. The prostate was firm and in one area it was quite hard.

A radical prostatectomy and seminal vesiculectomy were performed.

A pathological diagnosis of carcinoma of the prostate was made.

Comment: In this case, the bleeding was associated with a malignant lesion in the prostate. Bleeding, however, was one of the first symptoms. In spite of the radical operation, the patient now has a recurrence.

Final diagnosis: Carcinoma of the prostate.

Case 9: A woman, 56 years of age, entered the Clinic on April 26, 1937, complaining of blood in the urine. She stated that from time to time during

the preceding 2 years she had noticed traces of blood in the urine. There was no irritability of the bladder or other urinary symptoms.

Cystoscopic examination revealed a tumor on the left lateral wall of the bladder. Resection of the left wall of the bladder was performed on April 28, 1937, and a pathological diagnosis of carcinoma was made.

Comment: In this instance, only traces of blood appeared in the urine and for varying intervals of time gross hematuria did not occur. There were no other urinary symptoms.

The patient is living and well with no evidence of recurrence one and one-half years later.

Final diagnosis: Carcinoma of the bladder.

Case 10: A woman, 59 years of age, entered the Clinic complaining of blood in the urine and frequency of urination. Two weeks previously, pain on urination developed and she noticed the presence of blood in the urine. Bleeding was much less pronounced during the following week; however, the burning on urination and frequency persisted.

Urological examination revealed the presence of hemorrhagic cystitis.

Comment: In this case, the age of the patient would suggest that a malignant lesion might be responsible for the hematuria. However, complete urological examination revealed inflammation of the bladder to be the etiologic factor and this responded rapidly to treatment.

Final diagnosis: Hemorrhagic cystitis.

Case 11: A man, 44 years of age, entered the Clinic on November 20, 1935, complaining of blood in the urine.

About two weeks previously, following a severe cold and acute tonsillitis of several days' duration, he observed the presence of blood in the urine. There was no accompanying frequency or dysuria.

Complete urological study revealed the presence of a subacute glomerular nephritis (mild).

Comment: In this case, the history of the hematuria following a severe acute tonsillitis immediately suggested the possibility of nephritis. However, complete urological investigation was instituted to rule out the possibility of additional coexisting pathology.

Final diagnosis: Subacute glomerular nephritis (mild).

Case 12: A woman, 62 years of age, entered the Clinic on May 21, 1936, complaining of "rupture" and two attacks of blood in the urine.

The first attack of hematuria had occurred four years previously and the second one year later. The bleeding lasted about six weeks during which time blood was present in the urine daily. It then became intermittent and gradually stopped. No other urinary symptoms were elicited. The patient had had a rupture for 35 years which caused some pain on coughing and considerable distress.

Complete urological examination revealed a tumor of the left kidney. Nephrectomy was performed.

Comment: In this case, following the first attack of hematuria, the patient was well and free from symptoms for one year and after the second attack for 2 years. Her chief discomfort was due to the hernia which she wished

to have repaired. This case emphasizes the necessity for urological investigation in patients giving a history of hematuria.

Final diagnosis: Hypernephroma of left kidney. Hernia.

Conclusions

1. Hematuria is a symptom which requires early diagnosis. It should not be treated as a clinical entity.

2. Systemic disease, as well as lesions intrinsic in the genito-urinary tract, may account for the presence of blood in the urine.

3. In a series of 798 consecutive cases of hematuria reviewed from the records of the Cleveland Clinic, 59 per cent of the patients were suffering from new growths in the genito-urinary tract, renal tuberculosis, or calculous disease.

4. Complete medical and urological study may be required to establish an accurate diagnosis.

5. Hematuria with or without accompanying pain is frequently of grave significance and early determination of the responsible factors is required to render a good prognosis.

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