# Tubulointerstitial and Vascular Diseases

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## Tubulointerstitial Nephritis

### Mechanisms of Tubulointerstitial Nephritis

The tubulointerstitial compartment accounts for 80% of the renal mass [1]. It consists of renal tubuli, the tubular basement membrane, vascular structures, and interstitial cells as well as the surrounding extracellular matrix. The interstitial cells can be divided mainly into renal fibroblast cells and cells of the monocyte/macrophage system including dendritic cells [1]. The tubulointerstitial compartment is involved in the course of almost all renal diseases [2]. As a rule, changes begin with an interstitial inflammation that is the hallmark of tubulointerstitial nephritis (TIN). TIN can exist in an acute and a chronic form and can affect the tubulointerstitial space primarily or in the setting of primary glomerular or vascular diseases. All forms of interstitial disease are quite common. It has been estimated that up to 15% of all cases of acute renal failure (ARF) are caused by primary interstitial nephritis [3]. In addition, up to 25% of all cases of end-stage renal disease (ESRD) are attributable to primary chronic TIN [4]. According to the European Dialysis and Transplant Association (EDTA) registry, 20.2% of ESRD was caused either by pyelonephritis, interstitial nephritis, or toxic nephropathy. These forms are characterized by primary TIN [5]. More recent data, however, suggest a less prominent role, with about 4.5% of cases of chronic renal failure (CRF) in the US attributable to primary interstitial diseases [6]. Moreover, secondary tubulointerstitial injury is one of the most important factors for the outcome of primary glomerular and vascular diseases [7] because interstitial nephritis is the common pathway of almost all forms of progressive renal disease and one of the most common lesions in nephrology [8]. Immune response in interstitial nephritis can be antibody dependent or cell mediated but, in contrast to glomerular diseases, cell-mediated reactions predominate [9].

In TIN, T lymphocytes are the predominant infiltrating cells with a great abundance of CD4+ T helper cells (CD4/CD8-ratio often > 1). These T helper cells need MHC-class II (HLA-D) restricted presentation of responsible antigens to become activated. Antigen presentation in the renal interstitium can be provided efficiently by infiltrating macrophages and interstitial dendritic cells [10]. In addition, data on glomerular diseases suggest that tubular epithelial cells may serve as antigen presenters as well [11]. In interstitial nephritis, predominantly CD8+ T effector cells become activated in turn and result in renal tissue damage by 2 mechanisms: they can be cytotoxic due to the release of perforans, or they can lead to a delayed-type hypersensitivity reaction with the release of inflammatory

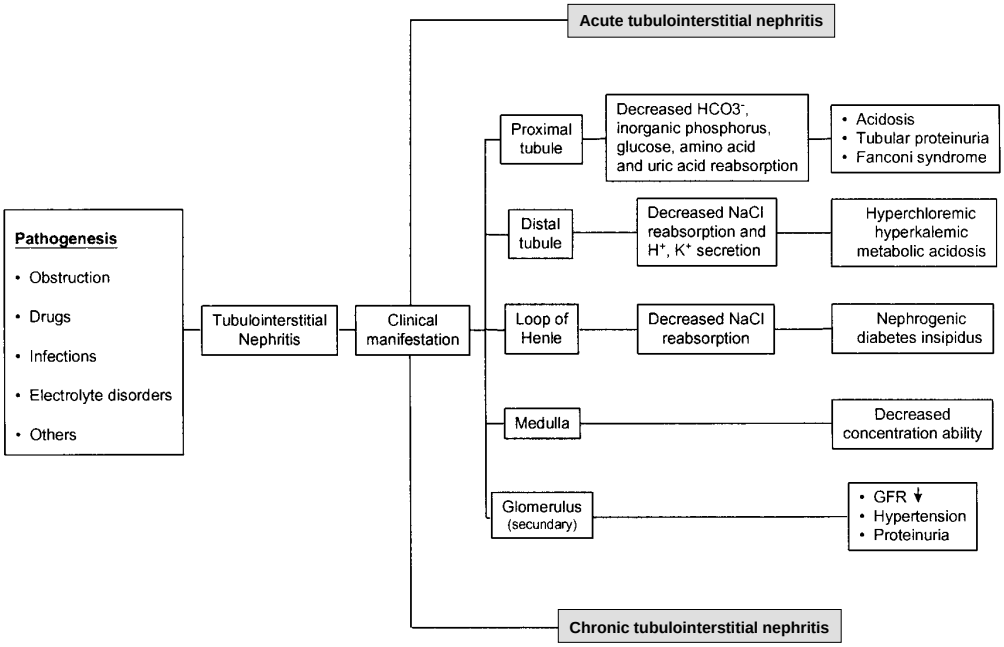


**Figure 1.** Pathogenesis and clinical manifestations of tubulointerstitial nephritis. Modified from [Kuhlmann U., Walb D, Luft FC: Nephrologie. 3rd ed., Thieme, Stuttgart 1998] with permission.

cytokines [12]. Only occasionally, deposition of immune complexes within the interstitium may be found, especially in patients with underlying systemic autoimmune disorders. In rare cases of specific antitubular basement membrane disease, linear deposition of immunoglobulin along the tubular basement membrane can be detected (additionally in up to 70% of cases with primary antiglomerular basement membrane (anti-GBM) disease). The target antigens for humoral immunity in human TIN remain poorly defined [13, 14]. Only the target antigen of experimental antitubular basement membrane (TBM) disease in mice has been characterized as glycoprotein 3M-1 and is secreted by proximal tubular cells [15, 16]. Apart from native renal antigens, drug/hapten conjugates, microbial antigens, and foreign antigens that induce cross-reactive immunity to autoantigens (molecular mimicry) are believed to be of importance in TIN. Irrespective of the type of immune reaction, in the course of sustained primary or secondary interstitial inflammation and tissue damage, activation of interstitial cells can initiate processes of interstitial proliferation and fibrogenesis that inevitably result in renal scarring and chronic renal failure.

Figure 1 summarizes the pathogenesis and clinical manifestations of TIN.

## Acute Tubulointerstitial Nephritis (ATIN)

ATIN is a heterogeneous disorder in etiology, clinical presentation, laboratory findings, and outcomes. The incidence of ATIN for cases of clinically encountered ARF is diffi-

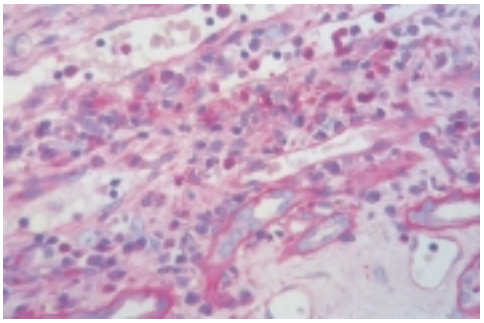

**Figure 2.** Acute drug-induced tubulointerstitial nephritis (ibuprofen) in a 60-year-old woman. Observe the dense lymph/plasma cell and eosinophil (characterized by their dark cytoplasm) infiltration (PAS, magnification x 400).

cult to establish. It has been estimated that up to 15% of all cases of ARF are caused by primary interstitial nephritis [3, 8]. The proportion of CRF attributable to ATIN is fortunately much lower, in the range of 1‰. ATIN is slightly more common among men than in women (about 2 – 3 : 1) and can be observed in any age. Elderly patients are more often affected, however, probably because of the more abundant use of drugs in this group.

## Pathology

The principal morphologic changes that characterize all forms of ATIN are interstitial expansion caused by edema and infiltration of inflammatory cells as well as pathological changes in the tubules. Usually, the glomeruli and renal vascular structures appear unaffected. The nature of the cellular infiltrate varies according to the underlying disease. In general, the infiltrating cell population is composed mainly of neutrophils, T and B lymphocytes, macrophages, natural killer (NK) cells, plasma cells, and eosinophils [9, 17 – 21] (Figure 2). The infiltrate is typically T lymphocytes and monocytes/macrophages [22] in interstitial nephritis associated with glomerular disease. The interstitial infiltrates are often diffuse, but focal patterns of injury are also seen. Granuloma formations may be found as well, and drugs are a common cause of these lesions in acute settings [23 – 25]. However sarcoidosis, granulomatous vasculitis, or tuberculosis should be considered in such cases [24, 26 – 28]. In cases of Wegener granulomatosis, glomerular and vascular structures are almost always involved [27]. The tubular changes range from cell swelling and vacuolization to tubular cell necrosis with disruption of the tubular basement membrane [20]. A marked expression of adhesion- and HLA-class-II molecules by tubular cells can be observed by immunohistochemistry and may be of great importance for the disease process [19, 29, 30]. In contrast to glomerular diseases, deposition of immunoglobulins or complement are of minor importance [17].

## Clinical Features

In ATIN, a rapid decrease in renal function is typical at presentation. A careful evaluation of the history is essential in this setting because most patients will be asymptomatic or will complain only of unspecific symptoms. For example, the clinician should be on the alert for a new medication, especially in the elderly patient, or systemic illness, particularly streptococcal infections in children. While there are no pathognomonic clinical findings in ATIN, certain systemic manifestations may point to the diagnosis if present. The classical descriptions of patients with methicillin-induced interstitial nephritis go back to the early 1960s. Systemic manifestations such as

- low-grade fever (70 – 100%),
- fleeting skin rash (30 – 50%), and
- diffuse arthralgias (up to 20%)

**Table 1.** Laboratory Features of ATIN

| | |
|---|---|
| Blood | Eosinophilia<br>IgE-Elevation |
| Proteinuria | < 3 g/day (exception: some cases of NSAID)<br>Tubular pattern (α1-microglobulin, β2-microglobulin, N-acetyl-beta-glucosaminidase) |
| Sediment | White blood cells (free and casts)<br>Microhematuria (rarely gross hematuria, red casts uncommon)<br>Eosinophiluria |
| Functional parameters | Glucosuria, aminoaciduria, hyperphosphaturia<br>Renal tubular acidosis (bicarbonate loss, impaired acid secretion)<br>Hyperkalemia<br>Salt wasting<br>Impaired concentration ability |

together with signs of ARF make ATIN a probable diagnosis [31].

However, the entire constellation has been reported in the minority of ATIN cases (4 out of 27 in one study) [32]. In most cases only nonspecific constitutional symptoms such as fever, fatigue, or nausea are present. In addition, some patients may complain of lumbar pain due to distension of the renal capsule from diffuse swelling of the kidney. In contrast to glomerular diseases, oliguria, edema, and hypertension are less common in ATIN. As a consequence of an impaired tubular reabsorptive capacity, polyuria and nocturia may develop. Long-term consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to a type of ATIN, accompanied by glomerular proteinuria sometimes severe enough to cause full-blown nephrotic syndrome. ATIN histologically characterized by granuloma formation within the interstitium can clinically appear months after drug ingestion. Typically, classic allergic symptoms are lacking. Therefore, diagnosis is often delayed in these cases, and progression to renal failure often occurs.

## Laboratory Findings

The first clinical presentation of ATIN is variable, and specific findings that point to diagnosis are often lacking. Several findings on blood and especially urine analysis may point of ATIN (Table 1). Elevated plasma creatinine and blood urea nitrogen (BUN) values should be investigated to discover the cause of impaired renal function. Especially in drug-related ATIN, further blood tests may reveal transient eosinophilia and elevated plasma IgE levels, but these findings occur only in about 30% of cases [33 – 35]. In addition, nonspecific elevations of C-reactive protein (CRP) levels and an accelerated erythrocyte sedimentation rate (ESR) may be present. In > 75% of cases, mild to moderate proteinuria and hematuria can be found [36, 37]. Proteinuria is tubular in the majority of cases. Nephrotic-range proteinuria is not usually found. However, NSAID-induced interstitial nephritis is often characterized by serious renal injury including the glomeruli (minimal change lesions). Hence, this form of ATIN may be accompanied by nephrotic syn-

drome [38]. Gross hematuria rarely occurs in ATIN, but careful examination of the urinary sediment is essential. In approximately 75% of patients, red and white blood cells (sterile pyuria) will be found [37]. Occasionally, white and red blood cell casts may be observed, but the latter strongly suggest a glomerular lesion. Eosinophiluria is suggestive of allergic interstitial nephritis. Eosinophils in the urine can be detected by either Wright's stain or Hansel's stain, the latter being approximately 5 times more sensitive [39, 40]. However, eosinophiluria can be observed in many other cases such as rapid progressive glomerulonephritis (GN), urinary tract infections (UTI), prostatitis, and atheroembolic disease, as well as in episodes of renal allograft rejection. Therefore, it may help to distinguish ATIN from acute tubular necrosis (ATN), but the positive predictive value of this parameter is < 40% according to recent studies [41].

As a consequence of tubular injury and interstitial inflammation, various tubular dysfunctions may be observed in the course of ATIN. Lesions affecting the proximal tubule may result in glucosuria, aminoaciduria, uricosuria, and hyperphosphaturia. A proximal loss of bicarbonate along with an impaired acid secretion within the distal segments can result in renal tubular acidosis. Hyperkalemia and renal salt wasting together with a reduction of renal concentration ability may point to a dysfunction of the distal tubule or collecting duct. In a report of 9 patients with biopsy-proven ATIN, isosthenuria was present in all patients with a mean urinary osmolality < 350 mOsm/L and a urine/plasma osmolality ratio of 0.9. Urinary sodium was > 40 mEq/L in 8 out of the 9 patients studied [42]. However, signs of tubule dysfunction such as Fanconi syndrome and renal tubular acidosis are rarely observed in the course of ATIN and are more common in patients with chronic tubulointerstitial disease.

**Table 2.** Etiological Factors of ATIN

| |
|---|
| Drugs |
| Infections |
| Idiopathic |
| Associated with Uveitis (TINU-Syndrome) |

## Diagnosis

Tubulointerstitial nephritis is a pathological phenomenon and not a clinical syndrome. Many features in clinical presentation and in laboratory analysis may suggest ATIN but only renal biopsy can establish the diagnosis with certainty in this setting. Therefore, renal biopsy should always be considered in any patients with ARF of unknown origin.

Ultrasonography is useful in the detection of ATIN. Because of the increased interstitial volume, the kidneys may appear swollen and the cortical echogenicity may be increased. Additionally, renal scanning with gallium-67 has also been reported to detect ATIN in some patients [35, 43]. This method is very sensitive; however, the specificity is relatively low. Therefore, this method is not reliable in identifying noninfectious interstitial nephritis [44].

## Etiology

The etiological factors that can lead to acute interstitial nephritis may be divided into 3 categories (Table 2). Drugs are the most im-

**Table 3.** Drugs Causing ATIN

| | |
|---|---|
| *Antibiotics* | *Diuretics* |
| Penicillins and derivatives | Thiazides |
| Cephalosporins | Triamterene |
| Azithromycin | Hydrochlorothiazide/ Amiloride |
| Chloramphenicol | Furosemide |
| Ciprofloxacin | Indapamide |
| Erythromycin | Chlorthalidone |
| Ethambutol | |
| Minocycline | *Miscellaneous* |
| Nitrofurantoin | Allopurinol |
| Polymyxin B | Azathioprine |
| Rifampicin | Captopril |
| Rolitetracycline | Carbamazepine |
| Spiramycine | Clofibrate |
| Sulfonamides | Interferon α |
| Tetracyclines | Interleukin-2 |
| Trimethoprim-sulfamethoxazole | Paracetamol |
| Vancomycin | Phenindione |
| Acyclovir | Phenobarbital |
| Foscarnet | Phenytoin |
| Griseofulvin | Propylthiouracil |
| | Streptokinase |
| *Nonsteroidal anti-inflammatory drugs* | Sulfinpyrazone |
| | Ticlopidine |
| | Triazolam |
| | Warfarin |
| *Anti-ulcer-medications* | Anti-CD4 antibody |
| Omeprazole | Hairy vetch poisoning |
| Ranitidine | |
| Cimetidine | |

**Table 4.** Infections Causing ATIN

| | |
|---|---|
| *Bacteria* | *Viruses* |
| *Brucella* species | Epstein-Barr virus |
| *Campylobacter* | Cytomegalovirus |
| *Corynebacterium diphtheriae* | Hanta virus |
| *Escherichia coli* | Hepatitis B virus |
| *Legionella pneumophila* | Herpes simplex virus |
| *Pseudomonas aeruginosa* | HIV |
| *Salmonella* | Rubeola |
| *Serratia marcescens* | Polyomavirus |
| *Streptococcus* | |
| *Staphylococcus* | |
| *Yersinia* | |
| *Others* | |
| *Histoplasmosis* | *Mycoplasma hominis* |
| *Leptospira* | *Rickettsia rickettsii* |
| *Leishmania donovani* | *Schistosoma mekongi* |
| *Mycobacterium tuberculosis* | *Toxoplasma gondii* |

portant causative agents, followed by systemic infections, particularly in children. Less common are autoimmune and systemic disorders or idiopathic origin [22].

## Drugs

With the introduction of sulfonamides in the 1940s, an association of nephritis with these substances was recognized. Classical reports of drug-induced ATIN are those with maculopapular rash, fever, and eosinophilia after the ingestion of methicillin [45 – 47]. Hence, most studies were performed on β-lactam antibiotics in the past. Currently, quinolones and proton pump inhibitors are the leading causative agents, followed by 5-aminosalicylate and NSAIDs. As drug-related ATIN seems to be due to a hypersensitivity reaction, it can be induced by virtually any drug. However, certain drugs are more prone to induce ATIN (Table 3).

Drug-induced ATIN may occur in a variety of forms (Figure 3). Depending on the drug involved and the individual response, the clinical symptoms can range from full-blown hypersensitivity (fever, rash, eosinophilia, and oliguric renal failure) to asymptomatic courses with only laboratory findings. Altogether, drug-induced ATIN should always be considered in patients with an abrupt deterioration of renal function and signs of tubular dysfunction.

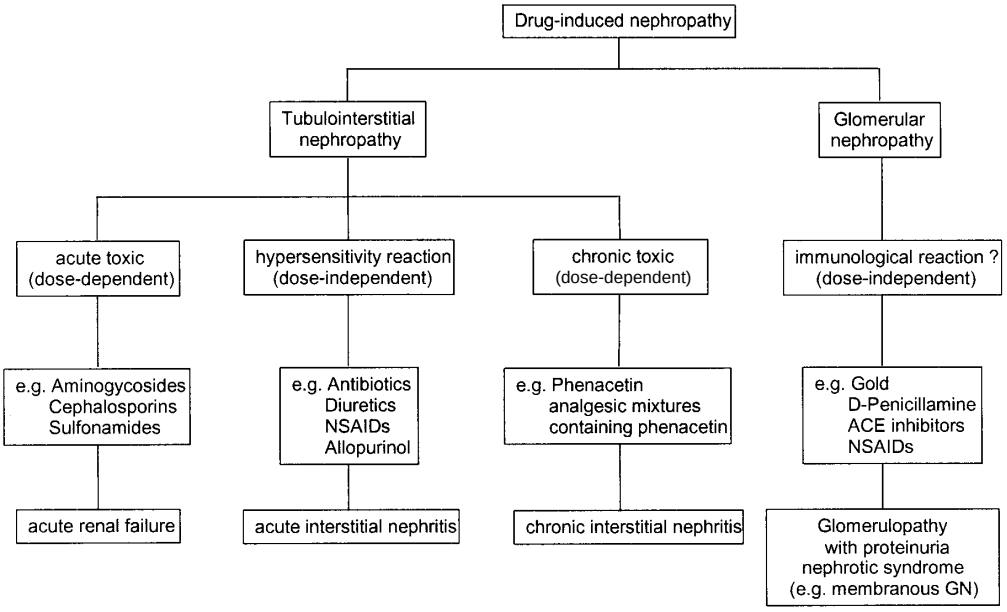


**Figure 3.** Drug-induced nephropathy. Modified from [Kuhlmann U., Walb D, Luft FC: Nephrologie. 3rd ed., Thieme, Stuttgart 1998] with permission

Infections

Infection-mediated ATIN (Table 4) is usually caused by an ascending infection with *Enterobacteriacae* (most commonly *E. coli*) and *Streptococcus faecalis*. In hospitalized patients, UTIs with other organisms such as *Serratia marcescens* or *Pseudomonas aeruginosa* are more common due to exposure to these bacteria and concurrent antibiotic treatment. Tubulointerstitial infections are dependent on the presence of urinary reflux and on bacterial virulence factors. Because of its high prevalence, the most extensively studied pathogen is *E. coli* [48]. One virulence factor that seems to be very important is the presence of fimbriae that enable the bacterium to adhere to epithelial cells [49]. P-fimbriae play an important role in first attacks of pyelonephritis due to their capability to mediate adhesion to human P blood group receptors [49]. Thus, although only 10 – 15% of all *E. coli* strains that cause UTI are P-fimbriated, 70 – 100% of all cases of nonobstructive pyelonephritis are caused by P-fimbriated *E. coli*. Another potential virulence factor is the presence of α-hemolysine [50]. The importance of all virulence factors seems to be linked to their neutrophil activation ability [48]. Polymorphonuclear neutrophils (PMN) may directly activate fibroblasts and thus cause interstitial fibrosis. However, experimental data to support this hypothesis are still lacking. Nevertheless, direct interaction of PMNs and fibroblasts has recently been demonstrated [51]. The role of lymphocytes and cytokines in acute and chronic phases of infection is not as well defined as in other forms of TIN. Nevertheless, it is known that even in infectious TIN T lymphocytes accumulate within a few days [52]. CD4+ from lesions in experimental pyelonephritis displayed MHC-restricted proliferative responses to a variety of *E. coli* and related strains, but not to other gram-negative bacteria [52]. Thus, it seems possible that many forms of chronic infec-

tious TIN are mediated by the same immune mechanisms as noninfectious forms. Cytokines that play a role in infectious TIN include interleukins IL-1 and IL-6, granulocyte-colony stimulating factor (G-CSF), granulocyte-monocyte-colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF)-α according to a study by Rugo et al. [53]. The role of obstruction itself is often underappreciated. Obstruction, albeit often the cause of chronic infection, can lead directly to tubulointerstitial injury. An increase in fibrogenic cytokines has been demonstrated in models of ureteral obstruction. For example, Kaneto et al. demonstrated increased transforming growth factor (TGF)-β1 mRNA expression in the tubules of rats with unilateral ureteral obstruction [54]. Moreover, sterile urine reflux caused cortical tubulointerstitial scarring in pigs [55], a mechanism potentially initiated by the extravasation of Tamm-Horsfall glycoprotein at high backflow pressures [56]. Another form of ATIN is observed in systemic infections in which there is no evidence of direct parenchymal invasion by an organism. However, the pathogenesis of this entity is unknown.

### Idiopathic ATIN

In a proportion of cases, no etiological factors can be identified. This form of ATIN cannot be distinguished from other forms by any specific symptoms or other characteristic findings [57]. In most cases it is reversible. Pathologically, mononuclear cells predominate within the interstitium. However, the resulting lesions are heterogeneous and occasionally, as with other clinical settings, anti-TBM-antibodies can be found. Thus, the idiopathic form(s) of ATIN can only be distinguished from other forms by exclusion of infections, history of drug ingestion, or immune disorders.

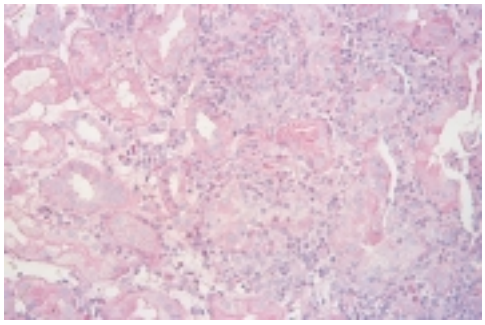

**Figure 4.** Tubulointerstitial nephritis in a 17-year-old girl with TINU syndrome. The interstitium shows dense lymph/plasma cell infiltration with focal tubulitis. Some eosinophils are scattered in between (PAS, magnification x 200).

The association of acute tubulointerstitial nephritis and acute uveitis observed in several patients (in adolescent girls or occasionally in adults) has led to the identification of a specific syndrome with a very particular symptomatology and course, the so-called tubulointerstitial nephritis/uveitis (TINU; Figure 4). The etiology of TINU syndrome remains to be elucidated but a recent report suggests underlying infection with *Chlamydia*. The prognosis of TINU seems to be excellent in younger patients, with or without steroid treatment. In adults, however, CRF ensues in a substantial proportion [58, 59, 60].

### Course and Treatment

The clinical spectrum of ATIN ranges from mild and short to severe cases with oliguric renal insufficiency. The primary therapeutic step in ATIN is to identify and withdraw the drug or offending agent, or to treat the underlying infection. Most patients will recover fully from renal failure within several days. In cases of ongoing and progressive renal insufficiency, a kidney biopsy should be performed to exclude other diseases (e.g. myeloma kidney, rapid progressive glomerulonephritis, or atheroembolism).

Although corticosteroids have been reported to be beneficial in some patients [31, 61], controlled clinical trials are not yet available. In the absence of a prompt response after withdrawal of a drug or offending agent, Kelly and Neilson suggest a trial of corticosteroids (1 mg/kg/day prednisone) in patients without infection. Improvement in renal function should begin within 1 – 2 weeks of initiation of treatment, in which case the course can be discontinued after 4 – 6 weeks [62]. If no improvement is seen within the first 2 weeks, an additional therapy with cyclophosphamide (2 mg/kg/day) with appropriate monitoring of the white blood cell count should be considered [62]. If successful, this regimen should be continued up to one year. When no evidence of improvement exists after 6 weeks, the combined therapy should be discontinued [62].

Most patients will have complete recovery of renal function within one year. However, up to one-third of patients with drug-induced acute interstitial nephritis (and more in the case of rifampicin) require dialysis treatment before resolution of the disease [62].

## Chronic Tubulointerstitial Nephritis (CTIN)

### Pathology

The pathological findings in patients with chronic forms of tubulointerstitial nephritis display characteristic changes in interstitial architecture observed in virtually all forms of chronic renal injury, e.g. of primary glomerular, vascular, cystic, or interstitial origin [7, 21]. Interstitial fibrosis along with tubular atrophy are the hallmarks of chronic interstitial disease. As an expression of ongoing inflammation, mononuclear cell infiltrates

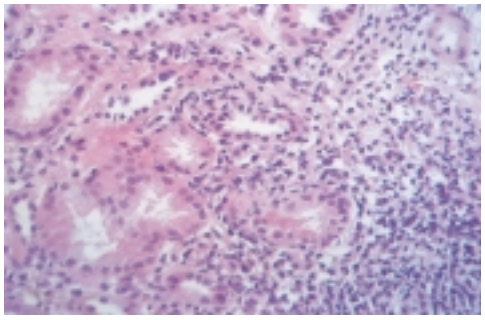

**Figure 5.** Secondary tubulointerstitial nephritis in Sjögren's syndrome, 68-year-old woman. Focally dense lymph/plasma cell infiltration (PAS, magnification x 400).

(mainly lymphocytes) in the interstitium and within the tubular epithelium (tubulitis with resulting cellular casts) can be seen (Figure 5). Although in CTIN the glomeruli mainly remain unaffected by the primary lesion, signs of secondary glomerular injury may be found as the disease progresses towards ESRD [10, 19, 63 – 65].

### Clinical Features

Usually, CTIN does not cause any specific clinical symptoms unless a primary systemic disease is present. Hence, some cases are diagnosed because of findings in screening tests (abnormal urinalysis or elevations in plasma creatinine and BUN). However, many patients unfortunately present with nonspecific symptoms of chronic renal failure late in the course of the disease [66].

### Laboratory Findings

When patients with CTIN present late, they have marked impairment of renal function and typical laboratory findings of chronic renal failure. Earlier cases of CTIN may present

with nonnephrotic-range proteinuria of a predominant tubular protein pattern and microscopic hematuria as well as pyuria. Surprisingly, positive urine cultures can be found in as many as 28% of patients [66]. As with acute TIN, glucosuria, renal tubular acidosis (RTA), and concentration defects reflect the degree of tubular dysfunction. Anemia develops relatively early (compared to glomerular diseases), and systemic hypertension occurs in about 50% of cases.

## Diagnosis

Renal biopsy is the only means for definite diagnosis in all forms of TIN, whether acute or chronic. Neither clinical features nor laboratory findings are specific. In CTIN associated with a primary disease, diagnosis may be suggestive in many cases but biopsy is still of great value, especially for informed judgement on individual prognosis and required therapeutic decisions. Nevertheless, a thorough investigation of the patient's history will provide the only reasonable basis for diagnosis in many patients with established late-stage renal failure.

## Etiologic Factors

CTIN can occur in association with a variety of underlying primary diseases of diverse etiology. Table 5 gives a concise overview of common and rare causes of CTIN, which are discussed in more detail in other chapters.

### Endemic Nephropathy

Endemic nephropathy, so-called Balkan nephritis, is a form of CTIN that is endemic in areas of the Balkan states. Usually, the disease occurs in middle-aged adults and progresses slowly towards ESRD. No diagnostic tests are

**Table 5.** Causes of Chronic Tubulointerstitial Nephritis

| |
|---|
| *Hereditary Diseases* |
| Autosomal dominant polycystic kidney disease |
| Medullary cystic disease / Juvenile nephronophthisis |
| Metabolic Disorders |
| Hypercalcemia (nephrocalcinosis), Hypokalemia |
| Hyperuricemia |
| Hyperoxaluria / Cystinosis / Methylmalonic acidemia |
| *Drugs and Toxins* |
| Analgesics |
| Lithium |
| Cyclosporine |
| Cisplatin |
| Nitrosoureas |
| Chinese herbs |
| Cadmium / Lead |
| Germanium lactate citrate |
| *Immune Mediated* |
| Renal allograft rejection |
| Systemic lupus erythematosus |
| Wegener granulomatosis / Microscopic polyangiitis |
| Vasculitis (other) |
| Sjögren syndrome |
| Sarcoidosis |
| *Hematologic Disorders* |
| Multiple myeloma |
| Light chain deposition disease |
| Paroxysmal nocturnal hemoglobinuria |
| Lymphoma |
| Sickle cell disease |
| *Obstructive Disorders* |
| Tumors |
| Stones |
| Outlet obstruction |
| Vesicoureteral reflux |
| *Infections* |
| Direct infection |
| Malacoplakia |
| Xanthogranulomatous pyelonephritis |
| *Miscellaneous* |
| Endemic nephropathy |
| Radiation nephritis |
| Progressive glomerular disease |
| Primary biliary cirrhosis |
| Aging |
| Hypertension |
| Ischemia |
| Extracorporal shock wave lithotripsy |

available, and its cause remains unknown (environmental agents, infections, and genetic factors are proposed). A higher incidence of uroepithelial tumors is suggested in these patients. As with other forms of TIN, elevated excretion of tubular proteins (especially β2-microglobulin) as well as additional signs of tubular dysfunction can be observed early in asymptomatic patients [67]. At this time there is no specific treatment regimen that can alter the rate of progression towards renal failure. Thus, elimination of known progression factors is essential.

Sarcoidosis (M. Boeck)

Most commonly, aberrations of calcium metabolism, including hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis, are responsible for the renal manifestations of sarcoidosis (Table 6). Recent studies suggest that the calcium abnormalities are associated with high blood concentrations of calcitriol and that calcitriol may be synthesized by mononuclear macrophages in the granulomas [68]. Up to one-third of patients with sarcoidosis are reported to have granulomas within the renal interstitium, which may also produce severe derangements of renal function. GN can occur with sarcoidosis, although the pathogenesis remains unclear [69 – 72].

**Table 6.** Renal Manifestation of Sarcoidosis

| |
|---|
| 1. Disturbance of calcium metabolism |
| – Hypercalcemia and hypercalciuria |
| – Nephrolithiasis |
| – Nephrocalcinosis |
| 2. Granulomatous tubulointerstitial nephritis |
| 3. Different pattern of glomerular disease |

Clinically apparent kidney dysfunction is rare unless hypercalcemia and hypercalciuria are present (about 10 – 15% of all patients). Mild to moderate albuminuria, microscopic hematuria, and sterile pyuria predominate. A protein excretion of > 3 g/24hours may indicate a concomitant glomerular lesion. Hypertension is usually absent and renal size is well preserved. Urinary concentration defects (including nephrogenic diabetes insipidus), renal tubular acidosis, and inappropriate glucosuria may also be seen [73]. In patients with sarcoidosis-associated granulomatous TIN, renal disease is usually accompanied by other organ involvement. No factors are known to identify patients at high risk, but men are reported to be more prone to develop this entity. The findings in renal biopsy are distinct from other forms of TIN. Interstitial inflammation with noncaseating granulomas and epithelioid and multinucleated giant cells is the usual histologic picture (Figures 6a and 6b). There is no positivity for complement or immunoglobulins. Rarely, nonspecific glomerular or vasculitic changes can be observed. Pathologically, other granulomatous inflammatory processes like silicosis, tuberculosis, histoplasmosis, and Wegener granulomatosis or scattered infiltration by lymphoma cells (with reactive granuloma formation) may have to be distinguished in single cases. Interestingly, in a series of 6 patients with sarcoidosis and clinically significant renal insufficiency, 4 patients differed from the typical patient with sarcoidosis in that they lacked the usual clinical constellation of skin, eye, and pulmonary involvement [71].

The diagnosis is supported by clinical findings of sarcoidosis involvement of other organs and should be suspected on the basis of elevated or paradoxically normal serum calcium concentrations, due to increased plasma concentrations of calcitriol, while immunoreactive circulating parathormone concentra-

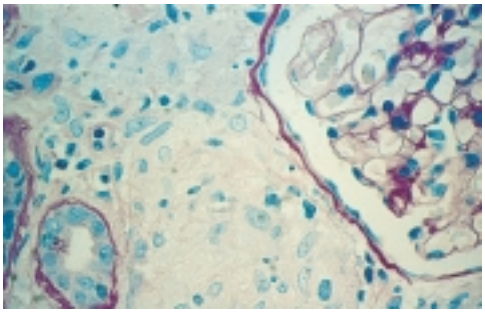

**Figure 6a.** Granulomatous interstitial nephritis in a 68-year-old man. Groups of histiocytes with one or more nuclei (PAS, magnification x 400).

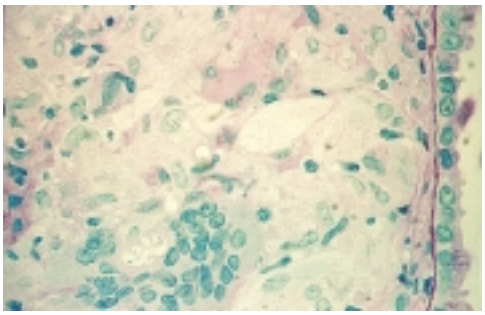

**Figure 6b.** Giant cell in the same patient (PAS, magnification x 400).

tions are depressed. An elevated 24-hour urine calcium concentration is consistent with the diagnosis but is not specific. Additionally, angiotensin-converting enzyme (ACE) activity is elevated in the serum in approximately two-thirds of patients with sarcoidosis. However, false-positive and false-negative results are common. Calcitriol as well as ACE could represent unregulated secretion products from granulomatous tissue, and their plasma concentrations may roughly reflect activity of the disease.

Response to corticosteroid therapy is often excellent, but in rare cases, the administration of cyclophosphamide may be of value when corticosteroids do not prove efficacious. Still, progressive interstitial fibrosis may result and these patients, a small subgroup of cases with nonresponding disease, may eventually develop CRF [62, 69, 71, 74].

## Analgesic Nephropathy

Analgesic nephropathy (AN) is a slowly progressive chronic renal disease characterized by renal papillary necrosis or calcifications and interstitial nephritis caused by excessive consumption of analgesic mixtures [75].

Since the discovery of an association between phenacetin use and the development of chronic interstitial nephritis, it has been recognized that drug-related renal disease is in large part a preventable disease. Discontinuation of heavy analgesic use may slow or stop progression of renal disease [76]. However, replacement of phenacetin with its major metabolite acetaminophen has not always been followed by a reduction in the incidence of analgesic nephropathy, suggesting that other drugs may play a role in this disease [77]. Several-case controlled studies and 2 prospective studies demonstrated the association between analgesic abuse and nephropathy [75]. However, the nephrotoxicity of the different analgesic products has not been clearly established [78]. The prevalence of analgesic nephropathy is related to the persistent daily consumption of widely available over-the-counter (OTC) mixtures containing 2 analgesic components plus caffeine and/or codeine [79]. This relationship could not be observed for analgesics containing only one analgesic component plus caffeine and/or codeine, although experimental data suggest nephrotoxicity of single analgesics [77, 78, 80]. The prevalence of analgesic nephropathy in patients with terminal kidney disease receiving dialysis varies widely between countries in Europe and outside Europe. In the early 1990s

the incidence was 0.8% in the US, 2% in Europe, and 9% in Australia [79]. In Scotland, Switzerland, Belgium, and Australia, it is a relatively common cause for chronic renal failure accounting for 10 – 20% of patients with ESRD. Recent analysis shows a changing pattern of prevalence and age distribution of analgesic nephropathy as a cause of ESRD. The EDTA registry reveals a declining incidence of analgesic nephropathy in the last decade in the age group under 64 years, while the incidence in the older age group remained high [81]. The same trends are observed in Australia [82]. These data indicate a real reduction in the incidence of analgesic nephropathy.

– *Pathology:* The pathologic abnormalities in analgesic nephropathy are nonspecific. The development from the earliest detectable lesions to end stage with bilateral shrinkage of the kidneys can be subdivided into the following 3 steps. The earliest detectable morphological lesion in patients with analgesic nephropathy is capillary sclerosis, which is found to be especially pronounced in the vessels of the renal pelvis and ureteral mucosa. The most pronounced capillary alterations are found in the proximal ureter. As a further morphological alteration, renal papillary necrosis follows. This lesion represents damage to the inner renal medulla that may be based on capillary sclerosis. Perhaps as a consequence of papillary necrosis, TIN may develop. Light microscopic investigations show a fibrotic interstitium with tubular atrophy and sporadic mononuclear cell infiltration. Sometimes concomitant focal glomerular sclerosis and interstitial calcifications can be found. At the time of clinical presentation, the kidneys are typically small [83 – 85].

– *Pathophysiology:* Experimental data show that the combination of acetylsalicylic acid with phenacetin or paracetamol induces severe medullary lesions more frequently than does either of these agents alone [77]. These results are in accordance with clinical and epidemiological observations in patients with analgesic nephropathy. The pathogenesis of analgesic nephropathy is related to the ability of the kidney to concentrate drugs in the papillae. For example, after ingestion of phenacetin and aspirin, phenacetin is converted in the gut and liver to acetaminophen by first-pass metabolism. Acetaminophen is normally metabolized in the liver and kidney by cytochrome P450 enzymes. After ingestion of large quantities, acetaminophen becomes concentrated in the papillae of the kidney during physiologic antidiuresis and undergoes oxidative metabolism by prostaglandin H synthase to biologically reactive intermediates. These are normally intercepted by reduced glutathione, which is present in excess within the renal cells. If acetaminophen is ingested alone, sufficient glutathione is generated in the papillae to detoxify the reactive intermediates [86, 87]. However, if acetaminophen is ingested with aspirin, the aspirin is converted to salicylate, which becomes highly concentrated in the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. The mechanism is not completely understood. However, the inhibition of NADPH production via the pentose shunt is a possible explanation. With the cellular glutathione depletion, the biologically reactive intermediates of acetaminophen then produce peroxides and arylation of tissue proteins, resulting in cellular dysfunction and necrosis of the

papillae [88, 89]. In addition, the inhibition of prostaglandin synthesis can exacerbate medullary damage from ischemia [90]. No evidence exists for the development of analgesic nephropathy with acetaminophen alone. Experimental data suggest that aspirin seems to be the most nephrotoxic of the commonly available analgesics and that combination therapy with aspirin is required for medullary damage in rats [91, 92].

– *Clinical Features*: The clinical course of analgesic nephropathy is frequently asymptomatic for years until the late stages of renal insufficiency. The earliest renal manifestation is caused by impaired tubular function. As a result of decreased urine concentrating ability, patients develop increased urinary frequency or urgency and nocturia. Additionally, an acquired form of RTA may contribute to the development of nephrocalcinosis. More than half of patients have pyuria, which, if persistently associated with sterile urine, provides an important clue to the diagnosis. Additionally, slight proteinuria may be present, whereas a protein excretion of more than 3g/24 hour may indicate a concomitant glomerular lesion. Macroscopic and microscopic hematuria may appear in the course of sloughing and elimination of fresh renal papillary necrosis, as a result of UTI, or, especially in the later stage, as a sign of uroepithelial carcinoma, which occurs with increased frequency in these patients. It is not known which analgesics predispose to carcinogenesis, seen after an average latency period of > 20 years [93, 94]. Therefore, even after termination of analgesic abuse, regular urine cytology and evaluation of the urinary tract should be undertaken for hematuria in these patients. Arterial hypertension is present in about 50% of patients with analgesic nephropathy. The hypertension seems to be renin dependent, because it may be exacerbated by volume depletion [95]. Additionally, acute papillary necrosis can evoke hypertensive crisis. Occasionally, shedding of papillary necroses into the efferent urinary tract may be associated with hematuria and even renal colic owing to obstruction of a ureter by necrotic tissue. Bacterial UTIs occur frequently and are late complications. With decreasing glomerular filtration rate (GFR), all metabolic signs of renal insufficiency may be present [95, 96].

  Besides the renal manifestations, a broad spectrum of extrarenal complications of chronic analgesic abuse can occur and often precedes the signs of analgesic nephropathy (Table 7). Women are affected 5 – 7 times more than men [95, 96].

– *Diagnosis:* Because there is no gold standard in the diagnosis of analgesic nephropathy, clues suggestive of the disease include a history of regular analgesic consumption, symptoms of an analgesic abuse syndrome, especially anemia, out of proportion to the degree of azotemia, renal colic without signs of nephrolithiasis, papillary necrosis, and sterile pyuria.

  CT scan without contrast medium is recommended to diagnose analgesic nephropathy in all patients with ESRD as well as those with mild and moderate renal insufficiency. The demonstration of bilateral decreased renal mass combined with either bumpy contours or papillary calcifications was found to have a high diagnostic value [97, 98].

– *Therapy:* There is no specific treatment for analgesic nephropathy. The primary goals of treatment are to prevent further

**Table 7.** Analgesic Abuse Syndrome

1. Nephropathy
   a) pathological findings
   – capillary sclerosis
   – papillary necrosis
   – tubulointerstitial nephritis
   b) clinical features
   – slowly progressive renal insufficiency
   – impaired tubular function
   – defect in urinary concentration
      – renal tubular acidosis
      – renal sodium loss
      – slight tubular proteinuria
   – hematuria
   – arterial hypertension
   – urethral obstruction
   – urinary tract infection

2. Uroepithelial carcinoma

3. Gastrointestinal complications
   – peptic ulcers and erosive gastritis
   – chronic pancreatitis

4. Hematological complications
   – anemia, out of the proportion to the degree of azotemia
   – mild hemolysis
   – methemoglobinemia (phenacetin)
   – agranulocytosis (pyrazolone derivates)
   – chronic hemorrhagic anemia (acetylsalicylic acids)

5. Skeletal complications, arthralgias

6. Typical skin color

7. Psychosomatic aspects
   – headache or chronic pain states
   – vegetative symptoms

renal damage. All suspect analgesics, particularly OTC medications, must be stopped to slow or stop progression of renal disease [76, 99].

The early treatment of complications, such as arterial hypertension, volume and sodium depletion, acute UTI, and urinary tract obstruction caused by renal papillary necrosis is important. Signs of kidney failure should be treated as appropriate for the extent and severity of the renal failure. Counseling, behavioral modification, or other interventions may assist in developing alternative methods for chronic pain control.

Patients undergoing renal transplantation as a result of analgesic nephropathy are at high risk of developing transitional cell carcinoma of the upper urinary tract. These tumors tend to be of high grade and stage, and affected patients have a poor outcome. Screening by urine analysis and voided urine cytology does not appear to be reliable for the early diagnosis of upper renal tract transitional cell carcinoma in the renal transplant patient. Therefore, annual cystoscopy and retrograde ureteric catheterization with washings, brushings, and radiological imaging should be performed to diagnose upper tract transitional cell carcinoma at an early stage. These patients should also be screened before transplantation using the same technique [100]. Considering the high mortality from urothelial carcinoma despite regular tumor screening in patients with analgesic nephropathy after renal transplantation, other investigators suggest that a bilateral nephroureterectomy should be performed prophylactically in patients with proven analgesic nephropathy [101].



## Multiple Myeloma

Multiple myeloma is a malignant proliferation of plasma cells characterized by excessive production of monoclonal immunoglobulins (IgG ≈ 53%, IgA ≈ 25%, or IgD ≈ 1%) or light chains (Bence-Jones proteins) (≈ 20%). Renal dysfunction occurs in > 50%

of patients and can precede the nonrenal manifestations. The clinical presentation is characterized by renal failure, which is a major cause of death. The kidneys of patients with multiple myeloma can be damaged by multiple mechanisms (Table 8) [102].

**Table 8.** Factors Contributing to Nephropathy in Patients with Multiple Myeloma

| |
|---|
| – Excretion of light chains which may cause the following renal diseases: |
| Myeloma kidney |
| Light chain nephropathy |
| AL-Amyloidosis |
| – Hypercalcemia |
| – Hyperuricemia |
| – Dehydration |
| – Recurrent infectious pyelonephritis |
| – Renal plasma cell infiltration |
| – Contrast media or nephrotoxic agents |

The myeloma kidney or cast nephropathy is the most common lesion resulting from light chain toxicity. It is characterized by large proteinaceous intratubular casts surrounded by multinucleated giant cells, probably of monocyte-macrophage origin [103]. The casts typically consist of Tamm-Horsfall protein and light chains [104]. As a consequence of cast formation, intratubular obstruction may develop. The tubules are extensively damaged and show tubular atrophy and fibrosis [105]. Additionally, plasma cell and mononuclear cell infiltration of the kidney, nephrocalcinosis, and amyloid deposits in the vessels and glomeruli may also be present. Light chain deposits can typically be observed by means of immunofluorescence staining in renal basement membranes (tubular, glomerular, and vascular) [106]. In addition, there is often concomitant deposition in the glomerular mesangium.

The pathogenetic causes of cast nephropathy are still unknown. When Bence-Jones proteins of patients with multiple myeloma or AL amyloidosis are injected into mice, the animals reproduce renal lesions identical to those observed in patients [107]. Myeloma casts develop in the distal nephron when cast-forming light chains bind to a specific portion of Tamm-Horsfall protein, secreted by cells of the thick ascending limb of the loop of Henle, to form an insoluble protein complex. Light chains are normally synthesized by plasma cells in excess of heavy chains. Because of their low molecular weight (approximately 22 kD), light chains are filtered at the glomerulus, reabsorbed by the proximal tubule, probably by receptor-mediated endocytosis, and catabolized [102, 108]. However, in the course of multiple myeloma and other diseases, light chain production is dramatically increased. With the increase in amount of light chains presented to the tubules, the proximal tubular reabsorptive capacity is overwhelmed, which leads to the urinary excretion of light chains as Bence-Jones proteins. The tubular damage results either directly from nephrotoxic effects of Bence-Jones proteins or indirectly from intrarenal obstruction from cast formation [105]. Interestingly, there are unexplained individual variations in the toxicity of Bence-Jones proteins [109, 110]. Some patients who excrete large amounts of light chains develop no renal dysfunction. Others show a nephropathy despite small urinary amounts of light chains.

A variety of factors modify the interactions between the light chains and Tamm-Horsfall protein and thus influence the development of renal failure [102, 111]. The coaggregation depends on the ionic environment and physicochemical factors, such as light chain concentration [112], isoelectric point [113], acidic intraluminal pH of the distal nephron [114], tubular flow rate [112], and presence of complete Tamm-Horsfall protein [115]. In-

**Table 9.** Factors Affecting Cast Formation [102]

| |
|---|
| – Concentration and type of Bence-Jones protein |
| – Concentration and carbohydrate content of Tamm-Horsfall protein |
| – Distal nephron milieu: |
| Sodium chloride concentration |
| Calcium concentration |
| Tubule fluid flow rate |
| Tubule fluid pH |
| Furosemide or radiocontrast agents |

**Table 10.** Renal Manifestation of Multiple Myeloma

| |
|---|
| – Bence-Jones proteinuria, glomerular proteinuria |
| – Acute or chronic renal insufficiency |
| – Tubular dysfunction |
| Fanconi syndrome |
| Renal tubular acidosis |
| Defect in urinary concentration |

creasing concentrations of sodium or calcium but not magnesium facilitate coaggregation [115]. Patients who excrete large amounts of Bence-Jones proteins in the urine are the most prone to renal failure. Some investigations suggest that cast-forming Bence-Jones proteins have isoelectric points > 5.1. This may explain the observation that aciduria independent of urinary flow rate increases the nephrotoxicity of Bence-Jones proteins [114] and that an acidic intraluminal pH of distal nephron may give an optimal environment for the precipitation [102]. Conditions in which the intraluminal flow rate are reduced, such as volume depletion, can accelerate tubular obstruction. Furosemide augments coaggregation and accelerates intraluminal obstruction in rats, possibly by increasing the intratubular sodium and calcium concentration [112].

Experimental data suggest that ionic interaction between Bence-Jones proteins and a specific peptide binding site on Tamm-Horsfall protein promotes heterotypic coaggregation [116]. However, the carbohydrate moiety of Tamm-Horsfall protein is also essential for coaggregation, perhaps by facilitating homotypic aggregation [116]. Deglycosylated Tamm-Horsfall protein does not coaggregate with Bence-Jones proteins and colchicine, which seems to remove the carbohydrate component of Tamm-Horsfall protein, thus prevents coaggregation of Tamm-Horsfall protein and toxic light chains in rats [112].

Table 9 summarizes the factors affecting cast formation.

– *Clinical Features:* Renal failure occurs in nearly 25% of patients, whereas renal dysfunctions occur in > 50% of patients. Recurrent bacterial infections, especially pyelonephritis, are presenting features in about 25% of cases. The clinical presentation of renal involvement in multiple myeloma is characterized by acute or chronic progressive renal insufficiency. However, according to the multifactorial pathogenesis of the renal dysfunction, clinical features are variable (Table 10). Proteinuria is found in 70% of all patients with multiple myeloma and may often be the initial symptom. It reflects overflow of monoclonal Bence-Jones proteins. Generally, there is very little albumin in the urine because glomerular function is usually normal. When the glomeruli are involved, the proteinuria is nonselective. The presence of a nephrotic syndrome and a monoclonal kappa or lambda light chain in the urine almost always indicates primary amyloidosis or light-chain depo-

sition disease, and a newly diagnosed albuminuria in patients with multiple myeloma is suspicious of AL amyloidosis. In addition, > 70% of patients show signs of tubular defects, such as impaired acidification or adult Fanconi syndrome, which is characterized by excessive increased urinary loss of glucose, phosphate, and all glomerular filtrated amino acids. In addition, loss of bicarbonate induces RTA (type 2 proximal RTA), and the urinary concentrating ability may also be diminished [109, 117 – 120].

– *Diagnosis:* The diagnosis of multiple myeloma should always be considered when a patient > 50 years of age develops renal failure and proteinuria of unknown origin. The classic triad of multiple myeloma is a bone marrow specimen containing > 10% atypical or immature plasma cells, lytic bone lesions, and a serum and/or urine M component. Additionally, multiple myeloma should be considered when renal insufficiency is accompanied by hypercalcemia, inadequate anemia, and/or elevated erythrocyte sedimentation rate (ESR). Characteristically, dipsticks for detecting proteinuria are not reliable at identifying light chains. However other qualitative techniques that depend on precipitation of protein, such as the sulfosalicylic acid (SSA) method, are useful in detecting Bence-Jones proteinuria. Thus, the constellation of a negative dipstick test and a positive precipitation test can be due to the presence of Bence-Jones proteins. This should be further evaluated by electrophoresis and immunoelectrophoresis. Typically, a decreased anion gap can be found in patients with multiple myeloma because the M component is cationic, resulting in retention of chloride. The kidneys are normal size on ultrasound.

**Table 11.** Potential Therapies for Cast Nephropathy [102]

| |
|---|
| – **Chemotherapy to decrease Bence-Jones protein** |
| – Plasma exchange to remove light chains from plasma |
| – Increase free water intake to 2–3 L/day as tolerated |
| – Treat hypercalcemia |
| – Avoid exposure to furosemide and radiocontrast agents |
| – Alkalinize urine |
| – Colchicine to decrease amount and carbohydrate content of Tamm-Horsfall protein |
| – Reducing agents that alter the light chain binding site on Tamm-Horsfall protein |

– *Therapy:* Treatment strategies for myeloma kidney (Table 11) are somewhat controversial. The principle of therapy has been chemotherapy to decrease production of the abnormal monoclonal immunoglobulins and immunoglobulin light chains. Clinical data indicate that plasma exchange associated with chemotherapy rapidly removes large amounts of light chains and improves both renal function and long-term survival expectancies of patients suffering from ARF due to multiple myeloma with Bence-Jones proteinuria [121, 122]. Little attention has been given to understanding and disrupting the pathophysiologic mechanisms involved in production of intraluminal casts. Noncontroversial elements include the supportive treatment of hypercalcemia (corticosteroids, hydration, 0.9% sodium chloride infusion, calcitonin, bisphosphonates) and hyperuricemia (allopurinol, hydration, urinary alkalinization). Adequate hydration is necessary (daily intake of 2 – 3 L of fluids as long

as there are no signs of renal failure or heart insufficiency) to keep the urine flow high. Additionally, the sodium chloride concentration in the distal nephron should be lowered. Experimental data in rats show that urinary alkalinization prevents renal failure from Bence-Jones proteins. However, comparable results in human patients are missing. Radiocontrast media and nephrotoxic agents should be avoided. Furosemide can increase distal tubular sodium chloride and calcium concentrations and can enhance, in a concentration-dependent fashion, toxicity of cast-forming proteins in vivo. Particularly in the setting of volume depletion, loop diuretics should be used with caution because of their capability to augment coaggregation of light chains with Tamm-Horsfall proteins. Experimental data in rats suggest that treatment with colchicine prevents aggregation of cast-forming Bence-Jones proteins, apparently by decreasing the excretion and removing the carbohydrate moiety of Tamm-Horsfall protein [112]. Colchicine, in daily doses of 1 – 2 mg, is standard therapy in preventing renal amyloidosis from familial Mediterranean fever. Colchicine in this dosage might also be efficacious in managing patients with cast nephropathy. Additionally, reducing agents such as cysteamine (beta-mercaptoethylamine) alter the tertiary structure of Tamm-Horsfall protein sufficiently to diminish subsequent binding to light chains. However, the possible role of colchicine and reducing agents in the management of myeloma kidney requires further clinical studies [102].

Kidney transplantation has been performed in a small number of patients with myeloma kidney. Although recurrence of cast nephropathy has been described, the results support the strategy of offering cadaver renal transplantation to carefully selected individuals who require long-term dialysis and whose myeloma is in remission after chemotherapy [123 – 125].

## Uric Acid

Hyperuricemia can cause different renal disorders (Table 12). The term gouty nephropathy is used for the chronic interstitial nephritis with hyperuricemia and gouty arthropathy. While it is commonly accepted that hyperuricemia can cause ARF this has not been unequivocally established for chronic interstitial disease [126]. Experimental data support the hypothesis that interstitial deposits of urate and uric acid in the kidney may be derived from intratubular deposits that react with the tubular epithelium and pass into the interstitium. Loss of tubular integrity may not be a prerequisite for crystal migration [127]. However, there are no convincing data to verify an association between an overproduction of uric acid and progressive renal failure. Moreover, it has been reported that lead intoxication may be the pathogenically relevant agent in gouty nephropathy [128]. However, many patients with impaired renal function present with high serum uric levels secondary to diminished GFR and tubular effects of diuretic drugs. Lowering of uric acid production could be important in these patients if hyperuricemia leads to acceleration of renal dis-

**Table 12.** Hyperuricemia-associated Renal Disorders

| |
|---|
| Nephrolithiasis |
| Acute renal failure in excessive overproduction |
| Gouty nephropathy |

ease. Besides encouraging water intake (urinary volume > 2 L/day), a restriction of alimentary purine, alkalization of urine, and allopurinol in doses adjusted to renal excretory function should be considered in patients with serum uric acid > 10 mg/dL (600 μM) [127].

Heavy Metal Intoxication

Chronic lead and cadmium exposure injure the proximal tubular cells initially. Hence, tubular transportation defects may be detected. However, as stated above, these findings are not specific in tubulointerstitial diseases. The pathogenetic mechanisms by which tubular lesions in heavy metal nephropathies result in chronic tubulointerstitial inflammation and fibrosis remain to be elucidated. Expression of pro-inflammatory mediators by injured epithelial cells may lead to mononuclear cell infiltration and activation of cytotoxic T lymphocytes. CTIN in chronic lead and cadmium intoxication will be discussed in more detail. In addition, intoxication with several other metals such as mercury, thallium, chromium, lithium, and nickel may lead to CTIN [129].

– *Lead Nephropathy:* Chronic exposure to lead can be associated with CRF displaying the pathological features of CTIN (see also above) [130]. Lead ingestion can arise from occupational exposure as well as from household sources (e.g. pottery, crystal, old water pipes). Lead accumulates in the $S_3$ portion of the proximal tubular cells, leading to dysfunction ranging up to full expression of the Fanconi syndrome [131]. Proximal tubular lesions are usually accompanied by additional chronic interstitial nephritis with interstitial fibrosis, atrophy, and nephrosclerosis [132]. Clinical signs of lead nephropathy are hyperuricemia and hypertension. Recurrent gout in the presence of CRF is a useful marker of chronic lead poisoning [133]. The diagnosis of lead nephropathy is based on an augmented urinary lead excretion (>0.6 mg/24hours) following EDTA administration (2 doses of 1 g), while blood lead levels are less useful to determine a chronic exposure [134]. EDTA chelation therapy is suggested thereafter until lead mobilization becomes normal again, with a favorable outcome in some cases. In contrast to the course in adults, lead exposure in children only rarely results in CRF [134].
– *Cadmium Nephropathy:* Occupational and less often environmental (itai-itai disease) [135, 136] excess cadmium exposure result in tubular injury and interstitial nephritis. Metallothionin-bound cadmium is pinocytosed into proximal tubular cells leading to proximal tubular dysfunction and especially to hypercalciuria. A high incidence of metabolic bone disease and complications due to nephrolithiasis are special features of this entity, often being the initial symptoms. The diagnosis can be confirmed by the finding of a high urinary excretion of cadmium. Besides symptomatic treatment of bone disease and complications, there are to date no specific therapeutic options in cadmium nephropathy. Large amounts of cadmium are stored within the liver and kidneys, and the half-life ($t^{1/2}$) is > 10 years .

Hypercalcemia

The kidneys can be affected in many ways by hypercalcemia. Elevated serum calcium levels and excessive hypercalciuria in diseases with high calcium turnover often lead to an acute deterioration of renal function. Increased cholecalciferol in sarcoidosis or in

patients with excessive vitamin D intake are less frequent causes than paraneoplastic calcium release due to parathormone-related peptide or bone metastases. Tubular transportation disorders with ensuing hypercalciuria are rare. In hypercalcemia, it is believed that direct vasocontractory effects, a reduction in glomerular filtration coefficient, and volume depletion due to a vasopressin-resistant concentrating defect result in a decline of GFR [137, 138]. Apart from acute effects on renal function, hypercalcemia may also lead to a deposition of calcium within the tubulointerstitium (especially medullary tubular basement membrane, collecting ducts, and finally throughout the interstitium), so-called nephrocalcinosis [63, 139]. These tubulointerstitial calcium lesions in turn lead to inflammatory infiltration and chronic tubulointerstitial disease. Nephrocalcinosis can be diagnosed either by ultrasonography or by computed tomography (CT) as well as by plain X-ray imaging techniques. Diagnosis of the underlying disease is essential to enable specific treatment. Treatment and nonrenal complications of hypercalcemia itself are discussed in chapter I.5. In general, the outcome of acute deterioration of renal function is good if treated early depending on the cause of the hypercalcemia. In nephrocalcinosis, treatment results are less favorable than with all other forms of chronic tubulointerstitial disease.

### Hypokalemia

Chronic hypokalemia is another albeit rare electrolyte disorder that can cause tubulointerstitial nephritis. Inherited forms of hypokalemia are primary renal tubular transportation defects that lead to wasting of potassium into the tubular lumen (often accompanied by acid-base disorders and other defects). These forms of CTIN usually show slow progression towards ESRD. Hypokalemia nephropathy is characterized morphologically by vacuolization of proximal tubular cells, the origin of which is unknown. In addition to the histologic findings of chronic tubulointerstitial nephritis and fibrosis, periodic acid-Schiff (PAS)-positive intracytoplasmic granules and cyst formations within the renal medulla can be observed. Functionally, hypokalemia can lead to marked polyuria that is resistant to antidiuretic hormone (ADH). Experimental data in rats reveal that excessive synthesis of ammonia may initiate an inflammatory response, with tubulointerstitial damage caused by concurrent complement activation [140]. Potassium repletion is essential and can reverse both functional and structural abnormalities in many cases.

### Oxalosis

Hyperoxaluria can be caused by at least 2 hereditary disorders of oxalate metabolism: excessive oxalate load or an increase in bowel absorption of oxalate. Though relatively rare, inborn oxalate disorders often result in chronic renal disease and early end-stage insufficiency. Primary hyperoxaluria (PH) type 1 is characterized by the deficiency of the liver enzyme alanine glyoxylate aminotransferase, and the very rare PH type 2 is based on a defect of the D-glycerate dehydrogenase [141, 142]. Patients with lesions of large portions of the small bowel, especially the terminal ileum in inflammatory bowel disease, or with short bowel syndrome after surgery may have increased absorption of oxalate. An increased bile acid load in the large bowel is believed to capture calcium from calcium-oxalate complexes, thereby releasing free oxalate for absorption. In addition, ethylene glycol poisoning or ascorbic acid overdoses can result in excessive metabolic oxalate production and tubulointerstitial damage. Deposition of cal-

cium-oxalate crystals in many tissues and organs is the pathogenically relevant lesion. Besides renal involvement, deposition in the bones, in arteries, and in nervous tissue results in severe lesions that lead to a clinically prominent bone disease with fractures, ischemic damage, and polyneuritis as well as retinal lesions. In the kidney, nephrolithiasis, obstruction of the tubular lumina, and interstitial deposition of crystals are the main manifestations. Measures to lower oxalate often are ineffective to prevent CRF (and extrarenal damage). The most effective prophylactic treatment is increasing urinary output by augmenting water intake to 3 – 4 L/m$^2$/day. Administration of citrate, orthophosphate, or magnesium can prevent crystal formation and should be given additionally. Some cases of PH type 1 also respond to pyridoxine (a cofactor of enzyme activity). Patients with ESRD due to PH type 1 are reported to benefit from combined liver-kidney transplantation with good results in a number of cases associated with improvement of extrarenal manifestations [143, 144].

### Radiation Nephritis

Radiation nephritis has become rare during recent years because administration protocols for radiation were changed to lower the total dose on the kidneys when nearby target organs are to be treated. However, total body irradiation in patients receiving bone marrow transplantation is an increasing cause of radiation damage of the kidneys. Radiation nephritis is clinically divided into acute forms with a clinical onset within one year and more delayed reactions to radiation after several years.

Acute forms present with hypertension and chronic anemia as well as edema. In most cases, a progressive renal insufficiency will result in ESRD. Occasionally, varying degrees of proteinuria and microscopic hematuria are found. Especially in children, acute radiation nephritis may be associated with intravascular hemolysis, making differentiation from the hemolytic uremic syndrome (HUS) difficult.

In chronic forms, patients may present with often isolated hypertension or mild proteinuria even after more than a decade. Malignant hypertension can occur, probably due to lesions of the renal arteries, at least in some cases. Severe forms of CRF with hypertension and proteinuria can also be seen.

Histologic lesions of chronic tubulointerstitial fibrosis are found in radiation nephritis. Acute forms display signs of marked glomerular endothelial lesions as well. Inflammatory infiltrates are usually absent, probably secondary to the therapy and primary disease. The pathogenesis of radiation injury of the kidneys is believed to be primarily vascular with endothelial cell damage resulting in progressive vascular disease with ensuing tubular atrophy and generalized ischemic lesions of the tubulointerstitium. In addition, the tubular epithelium is affected primarily by irradiation. Recent data on fibroblast cell regulation suggest that parenchymal cells and especially fibroblasts may be in part responsible for fibrogenesis after radiation [145, 146]. As with other forms of progressive renal disease, administration of ACE inhibitors could prove advantageous [147]. Hypertension due to unilateral disease may respond to nephrectomy of the affected kidney. Radiotherapy involving the kidneys exacerbates the risk for renal toxic injury by nephrotoxic drugs (radiocontrast agents, antibiotics, and especially cytotoxic drugs). Hence, careful management of radiation along with additional therapy is necessary.

### Course and Treatment

In most forms of CTIN, the primary disease cannot be treated sufficiently (specific therapies of some special entities have been discussed before). Moreover, even if further renal injury can be prevented, renal function slowly but inevitably deteriorates towards CRF, once a certain degree of tubulointerstitial damage and especially fibrotic changes have occurred (in cases of CTIN as well as in essentially all chronic renal disorders). The most important maneuver is controlling blood pressure (lowest tolerable blood pressure ≤ 140/85 mmHg) preferably with ACE inhibitors unless otherwise contraindicated [148]. These drugs seem to possess a higher nephroprotective potency than other antihypertensive substances Angiotensin II type I receptor antagonists may prove comparably effective in the future [149]. To date, however, evidence for the nephroprotective properties of ACE inhibitors is only documented in type-I diabetes mellitus [150]. Thus, treating elevated blood pressure, irrespective of the individual antihypertensive agents, remains the main goal. In addition, treatment of accompanying abnormalities such as hyperuricemia, metabolic acidosis, and hyperphosphatemia is advisable. The impact of a low protein diet on the progression of CRF is not clear [151 – 153]. We advise our patients to restrict protein intake to 0.8 g/kg/day (plus urinary losses). However, great care must be taken to prevent a catabolic state in these patients.

## Vascular Diseases of the Kidney

A large variety of renal diseases are of vascular origin. They may be classified as lesions affecting the large blood vessels (renal artery and vein) or primarily the small vessels and capillaries of renal parenchyma. The latter disorders and subtotal renal artery stenosis associated with hypertension are discussed elsewhere in chapter I.21. Thus, this chapter will focus on diseases of the large vessels only, namely renal artery thrombosis and embolism, cholesterol embolism syndrome, and renal vein thrombosis. These entities are similar in that they are usually associated with acute failure of the affected kidney. Hence, depending on pre-existing renal function and the extent of the lesion (unilateral or bilateral), they may cause acute azotemia. Table 13 summarizes renal vascular diseases.

### Renal Artery Thromboembolism

The term renal artery thromboembolism implies thromboembolic phenomena to the main renal arteries and the development of thrombosis in the renal artery.

The source of thromboembolic phenomena is usually the left atrium in patients with atrial fibrillation or the left ventricle with wall-adherent thrombi, shortly after myocardial infarction [154 – 156]. Less often, embolism might arise from endocarditis-associated thrombotic lesions (bacterial or aseptic). Additionally, rheumatic valvular disease and prosthetic heart valves are predisposing factors [155, 156]. Incidences with paradoxical embolism from venous thrombi through asso-

**Table 13.** Renal Vascular Diseases

**Diseases of the renal artery and branches**
*Renal artery thrombosis*
- – Renal vascular hypertension / ischemic disease
- – Atheromatous
- – Fibromuscular dysplasia

*Renal artery embolism*
- – Atrial or ventricular embolism
- – Aortal origin
- – Septic embolism (endocarditis)
- – Lupus anticoagulant syndrome

*Dissection (aortal)*
*Cholesterol embolism syndrome*
*Large vessel vasculitis*
- – Takayasu
- – Polyarteritis nodosa

**Diseases of the small renal vessels**
*Small vessel vasculitis*
- – Wegener granulomatosis
- – Microscopic polyangiitis
- – Henoch-Schönlein purpura

*Renal allograft rejection*
*Radiation nephritis (see CTIN)*
*Lupus anticoagulant syndrome*
*Disseminated intravascular coagulation*
*Toxemia of pregnancy*
*Hemolytic uremic syndrome / thrombotic-thrombocytopenic purpura*

**Diseases of the renal vein**
*Renal vein thrombosis*
- – Nephrotic syndrome
- – Heparin-induced thrombopenia type II
- – Hyperviscosity syndromes (e.g. Polycythemia vera, Leukemias, Thrombocytosis)
- – Diseases of the clotting system (inherited, lupus anticoagulant syndrome, etc.)
- – Infiltration by tumor (e. g. renal cell carcinoma)

*Compression of the renal vein*
- – Lymphoma
- – Pancreatic carcinoma

*Oral contraceptives*

ciated right to left shunting are very rare [157]. Diseases such as tumors and aneurysms may result in embolism and must be considered [158, 159]. Percutaneous intraarterial catheterization and aortography can cause an embolism involving the renal artery and aorta [160]. Renal artery embolism is bilateral in up to one-third of cases.

Renal artery thrombosis (RAT) is much less common than renal artery occlusion by emboli [161]. The latter is usually superimposed on an atheromatous plaque (as in coronary thrombosis). In addition, intimal lesions of the renal artery arising from trauma or surgery as well as inflammatory injury can cause thrombotic occlusion [162]. Numerous other factors have been associated with RAT. For example, ACE inhibitors may induce RAT in patients with renal artery stenosis [163 – 165]. RAT can also be associated with erythrocytosis, factor V Leiden mutation, antiphospholipid syndrome, or elevated cyclosporine levels [166 – 169]. Spontaneous renal artery thrombosis is a rare phenomenon [161].

## Clinical and Laboratory Features

Initially, patients usually complain of a sudden onset of flank pain, abdominal or chest pain, nausea, and vomiting. Fever and chills may occur. The physical examination often reveals abdominal or flank tenderness, sometimes accompanied by clinical signs of peritoneal irritation. The extremities and central nervous system (CNS) should be carefully evaluated for signs of embolization. Considering the nonspecific symptoms, an early diagnosis of renal arterial thromboembolism is often difficult [170, 171].

Laboratory findings include leukocytosis, proteinuria, hematuria, and elevated levels of lactic dehydrogenase (LDH), serum glutamic-oxalacetic transaminase (SGOT), se-

rum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, and creatinine kinase (CK) [170, 172, 173]. CK isoenzyme assay for CK-MB may be falsely high, due to a release of CK-BB activity from renal tissue. Deterioration of renal blood flow results in acute oliguric failure of the affected kidney, which can be compensated from a functioning contralateral organ. Anuria suggests the presence of bilateral emboli. Another result of renal ischemia is renin release leading to arterial hypertension [174]. If the onset is rather slow and occlusion is subtotal, only hypertension may result.

Various techniques can be employed to establish the diagnosis. Dopplerultrasonography, perfusion scintigraphy, and CT scan as well as magnetic resonance imaging (MRI) with contrast agents are highly sensitive and specific techniques [175 – 179]. Intraarterial angiography is the definitive method for the diagnosis of renal artery thromboembolism [159]. However, this technique should be used only when a therapeutic intervention is planned because of the risk of ARF induced by contrast media.

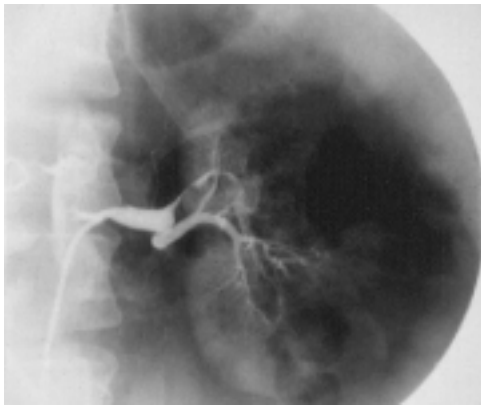

**Figure 7a.** Preinterventional intraarterial angiography of a 48-year-old-man with patent foramen ovale who had an embolism to the anterior main branch of the left renal artery. Consequently, renal perfusion was dramatically diminished.

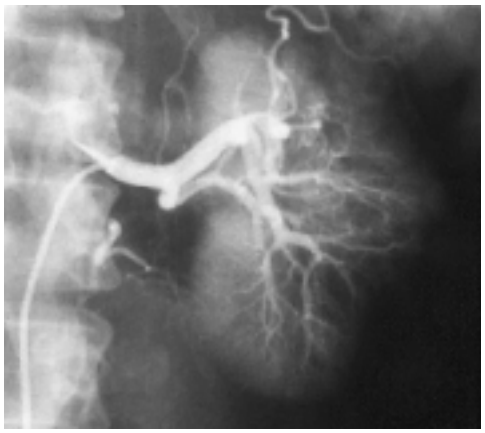

**Figure 7b.** Intraarterial angiography after successful intraarterial thrombolysis (urokinase) shows recanalization of the affected arterial branch and restoration of renal blood flow.

## Therapy

Intraarterial angiography allows immediate therapy in many cases. This will mean percutaneous transluminal angioplasty (PTA) and embolectomy with or without stenting of the vessel wall [180 – 182]. In some instances, vascular surgery will be needed. However, traditional methods of repair (e.g. in situ repair, bypass graft, and thrombectomy) have poor success rates. Renal autotransplantation was successfully performed in a patient with bilateral RAT [183]. If none of these therapeutic options can be employed, intraarterial or systemic thrombolysis (e.g. streptokinase or urokinase) should be considered to prevent irreversible loss of the organ [154, 184, 185] (Figures 7a and 7b). In any event, therapy should be started as soon as possible [186]. However, even after a one day delay, renal function in some patients will still profit from therapy because renal parenchyma may be perfused via collateral vessels or by minimal flow rates through the affected vessel [187, 188]. Conservative treatment by anticoagula-

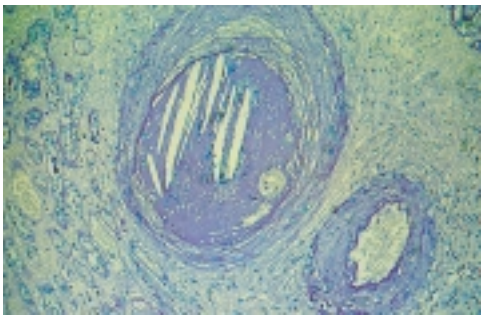

**Figure 8.** Renal cholesterol atheroembolism of an interlobular artery in a kidney transplant of a 70-year-old male. A fibrinous thrombus, containing typical cleft-like spaces of cholesterol crystals, is obstructing the lumen. Note edema and the ischemic tubular lesions in the surrounding interstitium (PAS, magnification x 125).

tion with heparin and acetylsalicylate is usually not sufficiently effective. However, long-term anticoagulation may be required in some patients to prevent embolization to other vital organs.

## Cholesterol Crystal Embolism

Cholesterol crystal embolism syndrome (CCE) occurs mainly in elderly patients (>60 years) frequently with a history of hypertension, atherosclerotic cardiovascular disease, renal failure, and aortic aneurysms (25%) at presentation (Figure 8). To a lesser extent, patients with thrombolytic or anticoagulant therapy are also affected. Possible predisposing factors are operative, radiological, and vascular procedures. Finally, there are reports that cholesterol embolism can occur spontaneously. Multiple showers of cholesterol emboli that stem from atheromatous plaques may lodge in medium-sized vessels (diameter < 200 μm). Here they initiate a progressive inflammatory reaction. Initially, an infiltrate of macrophages and giant cells is found. This is followed by a process of intimal proliferation and fibrosis and results in irreversible occlusion of the arteries [189 – 191].

### Clinical and Laboratory Features

CCE frequently presents with nonspecific manifestations that mimic other systemic diseases. The onset can be abrupt, but more chronic courses of progressive loss of organ functions can also be found. Clinical manifestations vary, depending on the affected organs, up to multiorgan failure. The brain, retinal arteries, and visceral vessels (pancreas, gut) are often involved. Also, embolism of muscles and skin is usually found. Thus, ischemic necrosis of the toes (blue toe syndrome) and livedo reticularis may occur and may be mistaken for vasculitis. In the kidneys, embolism results in deterioration of renal function and a mixture of mild proteinuria, microscopic hematuria, and leukocyturia. Additionally, nonspecific signs and symptoms such as fever, weight loss, myalgias, and headache may appear. Only one-third of CCE cases are diagnosed premortem, most commonly by biopsy of the muscle, skin, and kidney. Mortality is high and is most commonly due to multifactorial, cardiac, and renal etiologies. CCE should always be considered in elderly patients with atherosclerotic vascular disease with onset of renal insufficiency and cutaneous manifestations. In addition, thorough inspection of the retinal arteries may reveal cholesterol emboli. The emboli may be seen as bright copper yellow plaques, usually lodged at the bifurcations of retinal arterioles. In many cases however, the diagnosis will be missed unless renal biopsy demonstrates the presence of cholesterol emboli within the smaller arteries [190 – 192].

Laboratory findings are indistinct, but eosinophilia and increased ESR are often present.

Diagnosis of this disorder is difficult, as findings in urinalysis are rather nonspecific. Eosinophilia may be suggestive in combination with a history of predisposing procedures and skin findings [190 – 192].

## Therapy and Prognosis

To date, there is no specific treatment available, and CRF (as well as marked impairment from other manifestations) can often develop. Treatment of arterial hypertension may slow progression of renal insufficiency. ACE inhibitors may be beneficial to control arterial hypertension. Cholesterol-lowering agents are used as well [193]. They may stabilize the vascular plaque and therefore prevent further embolization. Prostacycline analogs are novel candidates for the treatment of cholesterol embolism [194]. The role of anticoagulation is controversial. It may predispose patients to the development of CCE [195]. Case reports of catastrophic cholesterol embolization temporally associated with thrombolytic therapy patients have suggested a causal relationship. The prevalence of cholesterol embolization in patients with acute myocardial infarction treated with thrombolytic therapy is not significantly higher than in those treated without thrombolytic therapy. Isolated case reports of severe cholesterol embolization temporally associated with thrombolytic therapy do not represent a phenomenon with widespread subclinical occurrence [196].

# Renal Vein Thrombosis

Thrombosis or occlusion of one or both renal veins occurs in a variety of settings (Table 14).

**Table 14.** Causes of Renal Vein Thrombosis

| |
|---|
| – Extrinsic compression (tumor, lymph nodes, aneurysm, retroperitoneal mass) |
| – Invasion of the renal veins or inferior vena cava by renal cell carcinoma |
| – Trauma |
| – Hemoconcentration (children in association with dehydration) |
| – Nephrotic syndrome |
| – Kidney transplantation (OKT3 and cyclosporine therapy) |
| – Steroid administration |
| – Pregnancy or oral contraceptives |
| – Constitutional protein S deficiency [197] |
| – Acute pyelonephritis [198] |
| – Primary antiphospholipid syndrome [199, 200] |

The association between renal vein thrombosis (RVT) and nephrotic syndrome was first described by the French nephrologist Rayer in 1840 [201]. In the past, most cases of RVT were diagnosed postmortem. Later, with the development of more advanced imaging techniques and selective catheterization, antemortem diagnosis of RVT was made possible and the number of described cases increased. So far, however, there is controversy about the real incidence of RVT in adults with the nephrotic syndrome. The incidence of RVT in the adult population is difficult to establish, because RVT frequently occurs without a specific clinical presentation, and therefore the diagnosis is often missed.

Thromboembolism is one of the most serious complications of the nephrotic syndrome [202, 203]. The most frequent site of thrombosis is the renal vein, with a reported incidence varying from 2 – 42% (average incidence 9%) [204]. The prevalence of RVT in patients with all types of nephrotic syndrome other than membranous nephropathy (MN) who were submitted to venography was 13% [204]. On the other hand, the mean frequency of RVT in patients with the nephrotic syndrome caused by MN was 15.4% (5 – 62%)

and increased to 29.6% when renal venograms were performed [204]. It is generally accepted that MN is the most common nephropathy associated with RVT. Other forms of nephropathy such as membranoproliferative glomerulonephritis (MPGN), lupus nephritis, and amyloidosis are not frequently associated with RVT [205]. For poorly understood reasons, nephrotic syndrome due to diabetes mellitus, focal sclerosis, and minimal change disease does not carry a high risk of RVT. It remains unexplained why there is a selective association between MN and RVT that does not completely exclude a possible pathogenetic correlation between primary RVT and the subsequent MN in selective patients [204]. It seems that the disease process underlying the nephrotic syndrome may play a paramount role in the genesis of RVT or thromboembolic phenomena [205]. In addition, RVT is very frequently complicated by pulmonary emboli. Approximately 42% of all patients with the nephrotic syndrome have thromboembolic complications that were more frequent in MN compared with other types of the nephrotic syndrome [204].

RVT is thought to be a result of the profound metabolic disorder due to the nephrotic syndrome. Alterations of many coagulation factors and clotting inhibitors as well as defects in the fibrinolytic system and platelets may arise. Table 15 summarizes the major factors that may contribute to the hypercoagulable state in the nephrotic syndrome [203, 204, 206].

In summary, the hypercoagulable state of the nephrotic syndrome seems to be characterized by occasionally low zymogen factors, a marked increase in cofactors, an increase in plasma fibrinogen, sometimes a decrease in antithrombin III, and an increase in $\alpha$ 2-antiplasmin. Additionally, thrombocytosis and increased platelet aggregation are observed. However, none of the various laboratory tests used so far can predict the development of thrombotic complications [207]. Additionally, hypoalbuminemia also might play a role in the platelet hyperaggregability in the nephrotic syndrome because albumin normally binds arachidonic acid, thus limiting its conversion to thromboxane A2 by platelets. Hypoalbuminemia might cause increased platelet archidonic acid metabolism, and therefore platelet hyperactivity may result [208]. As a consequence of these abnormalities in blood coagulation, a hypercoagulable state may develop. In addition, further clinical events or individual predisposition such as increased blood viscosity, intravascular volume deple-

**Table 15.** Major Factors Contributing to the Hypercoagulable State in the Nephrotic Syndrome

| Coagulation factor | Abnormality |
|---|---|
| Zymogens | Factor XII ↓<br>Factor XI ↓↑<br>Factor IX ↓↑<br>Factor VII ↓↑ |
| Cofactors | Factor V ↑<br>Factor VIII ↑ |
| Fibrinogen | ↑ |
| Fibrinolytic system | Plasminogen ↓<br>Plasminogen activator ↓ |
| Regulatory proteins | Antithrombin III ↓<br>alpha 2-antiplasmin ↑<br>alpha 2-macroglobulin ↑<br>alpha 1-antitrypsin ↓<br>protein C ↑<br>protein S ↑ |
| Platelets | Count ↑<br>Adhesiveness ↑<br>Aggregation ↑ |
| Endothel | Altered endothelial-cell function |

tion, or other therapeutic maneuvers (e.g. steroid therapy, diuretics) may trigger the disease.

## Clinical Features

Only 10% of patients with RVT present with clinical symptoms [203]. Acute RVT should be considered whenever an acute change in renal function or increase in proteinuria is noted in a setting of nephrotic syndrome. A sudden onset of persistent flank pain, which may be colicky at times, marked costovertebral angle tenderness, macroscopic hematuria, changes in urinary protein excretion, and increased renal size are features of acute RVT superimposed on nephrotic syndrome. When acute RVT arises bilateral, acute decline in GFR and marked oliguric ARF may develop. On the other hand, chronic RVT may frequently be clinically silent. The presence of pleuritic pain or hemoptysis in a patient with NS should alert the clinician to the possibility of RVT and pulmonary emboli. Additional clinical signs of RVT may be back pain, thrombophlebitis in the lower extremity, asymmetric edema, left varicocele, and dilated abdominal veins. Greatly elevated urinary fibrin-fibrinogen products may be helpful in screening for RVT in asymptomatic nephrotic syndrome patients [209, 210].

Color Doppler ultrasound is already the modality of choice for the detection of acute RVT [211, 212]. This noninvasive technique essentially measures the renal venous flow velocity. CT together with intravenous infusion of contrast media also allows a noninvasive evaluation of RVT [213]. Renal magnetic resonance angiography is also a noninvasive method for diagnosing RVT [214]. A major potential advantage in using this technique is the avoidance of iodine contrast media. Confirmation of RVT may be obtained by arteriography with delayed films during the venous phase, by inferior venacavograms, or, preferably, by selective renal venography. However, when renal function is normal, the high rate of renal blood flow leads to a rapid wash out of the contrast media and therefore may render the venography procedure difficult. Digital subtraction venography also seems to be a simple, safe, noninvasive, and quite efficient method to diagnose RVT [215].

## Therapy

The treatment of RVT is usually conservative with the use of heparin (clotting time 2 – 2.5 times normal) followed by oral anticoagulation (warfarin) or antiplatelet drugs [216]. Anticoagulation may be of prophylactic value for the occurrence of pulmonary emboli. Additionally, in patients with acute RVT, anticoagulant therapy reduces massive proteinuria and improves renal function in association with demonstrable recanalization of renal veins [217 – 219]. In most cases of chronic RVT, however, anticoagulant therapy has little effect on renal function, and thrombosis may recur in the recanalized veins when the therapy is discontinued. Altogether, the impact on renal function caused by treating asymptomatic chronic RVT is undetermined, but anticoagulation for chronic RVT is associated with relatively few complications [202]. In cases of nephrotic syndrome caused by MN, the anticoagulant therapy should be administered as long as the patient has nephrotic proteinuria, an albumin level < 20 g/L, or both. In patients with other causes of chronic nephrotic syndrome, a more cautious approach may be indicated, and prophylactic anticoagulation should be considered only if the risk of thromboembolism is high [203]. Because of the increased platelet function, platelet-aggregation inhibitors (low-dose aspirin) are a rational choice, although no infor-

mation from controlled studies is available [203].

Thrombolytic therapy (streptokinase, urokinase) can be used safely as long as there are no contraindications. However, this therapy should be reserved for those patients with the most severe disease or worse prognosis and seems to be warranted in the presence of bilateral RVT with ARF, massive clot size with high risk of acute embolic events, or recurrent pulmonary emboli [220 – 222].

The value of surgical thrombectomy in acute RVT has not been determined. However, this procedure may be useful in patients with acute RVT when complications develop such as pulmonary embolism and inferior vena cava thrombosis, right renal vein thrombosis without collateral flow, and acute RVT with shock, and patients are not otherwise expected to survive the acute episode [223].

Whether the high incidence of thromboembolic events in patients with the nephrotic syndrome justifies prophylactic administration of oral anticoagulants remains controversial. A carefully performed Markov-based decision analysis has concluded that for nephrotic patients with MN, the benefits of prophylactic anticoagulation outweigh the risks such as serious bleeding events [224]. However, decision analysis models do not replace the need for prospective, randomized clinical trials. Altogether, it may be prudent, unless contraindicated, to recommend long-term oral anticoagulation to nephrotic patients with MN, when the nephrotic syndrome is anticipated to persist. Additionally, when serum albumin concentration falls < 2.0 – 2.5 g/dL (high risk of thromboembolic events), prophylactic oral anticoagulation seems to be indicated. Also, patients with a history of thromboembolic complications should receive long-term oral anticoagulation. Immobilized nephrotic patients should probably receive short-term, low-dose parenteral heparin during their immobilization followed by oral anticoagulation [224, 225].

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