Drug induced glomerular diseases

Essay

An essay for partial fulfillment of Master Degree of Internal Medicine

By

Ahmed Abd El Rhman El sayed Hefnawy
M.B.B.Ch
Faculty of medicine-Benha University

Supervisors

Prof.Dr.: El Metwaly Lotfy El Shahawy
Professor of internal medicine and nephrology
Faculty of medicine-Benha University

Prof.Dr.: Mohammad El Sayed Salem
Professor of internal medicine and nephrology
Faculty of medicine-Benha University

Prof.Dr.: Ashraf Talat Mahmoud
Professor of internal medicine and nephrology
Faculty of medicine-Benha University

Dr.: Mohammad El Tantawy Ibrahim
Lecturer of internal medicine and nephrology
Faculty of medicine-Benha University

Faculty of Medicine
Benha University
2017
قُلِوا
سِلَانِكِ اللَّهُ إِلَى أَنْتَ الْقَدِيمُ
إِلَّا مَا غَلِبَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْبَصِيرُ
سورة البقرة الآية: 32
First of all, great thanks to "Allah" the greatest, for helping me in my life and in this work.

No words can express my gratitude and thanks to Prof. El Metwaly Lotfy El Shahawy, Professor of Internal Medicine, Faculty of medicine, Benha University for his valuable time, great help and continuous encouragement. It is of great honor to work under his guidance and close supervision.

My thanks and deepest gratitude to Prof. Muhammad El Sayed Salem Professor of internal medicine, Faculty of medicine, Benha University for his continuous support and helpful suggestion. Without his effort this work would not appear in this form.

My thanks and deepest gratitude to Prof. Ashraf Talaat Mahmoud Professor of internal medicine, Faculty of Medicine, Benha university, for his continuous encouragement and advice, I owed too much to him. His finger prints can be detected over each part of this work.

Many thanks and deepest gratitude to Dr. Mohammed El Tantawy Ibrahim Lecturer of internal medicine, Faculty of Medicine, Benha University, who kindly assisted in completion of the work and for his valuable help and support.

I wish to thank my family for their kind help and support throughout the work.
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<td>ESRD</td>
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<td>Nephrogenic diabetes insipidus</td>
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<td>NMR</td>
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<td>PCR</td>
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<td>TGF</td>
<td>Transforming growth factor</td>
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<td>TMA</td>
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<td>Vwf</td>
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Introduction

Drugs are frequently associated with the development of various types of acute kidney disease and chronic kidney disease (CKD). Although medication are a widely known cause of tubulointerstitial damage, drug related glomerular injury is not well appreciated but nonetheless important (Jai et al., 2015).

Establishing that a drug has caused an adverse event faught with challenges, but there are many methods to link specific drugs with an adverse drug reaction including exclusion of other agents, rechalleng, singularity of drug (i.e, no other potential offending agent used) and quantitation of drug level when possible (Merkel et al., 2001).

The glomerulus is a specialized structure which is composed of cells (epithelial, mesangial, endothelial) and matrix (mesangium, basement membrane) in a complex network of capillaries. Injury to these various components of the glomerulus produce various clinical syndromes. For example, podocyte (visceral epithelial cell) injury leads to nephrotic syndrome, capillary basement membrane alterations manifest as hematuria with or without proteinuria, while more destructive (necrotising /crescentic) acute lesions give rise to the syndrome of rapidly progressive glomerulonephritis (Aktar et al., 2004).

Drug-induced glomerular Injury: Direct cellular injury

A growing body of literature highlighted the potential for drug-induced glomerular lesion. The three primary pattern of drug-induced glomerular diseases stratified by cell type at which the glomerular lesion is focused: visceral epithelial cell injury, endothelial cell in injury, and mesangial cell injury. A number of commonly prescribed medications, including interferon (IFN), bisphosphonates, nonsteroidal anti-
inflammatory drugs (NSAIDs), antiplatelet agents, antiangiogenesis drugs, that are both prescribed and available over the counter, have been implicated in these iatrogenic forms of glomerular disease \((\text{Glen et al., 2015})\).

**Epithelial cells (podocyte)**, injury consists of minimal change disease which may be caused by IFN, pamidronate, lithium, and NSAIDs, and focal segmental glomerulosclerosis (FSGS) including both FSGS not otherwise specified (FSGS- NOS) and collapsing FSGS (C-FSGS) which may be caused by IFN, pamidronate, lithium, sirolimus, anabolic steroids. It is notable that, although the relationship between minimal change disease (MCD) and FSGS has been an area of long standing debate and the majority of patients of MCD do not progress FSGS or vice versa, multible therapeutic agents are associated with both conditions \((\text{Markowitz et al., 2010})\).

**Endothelial cell injury**, thrombotic microangiopathy (TMA) is a term that has been applied to multible seemingly unrelated conditions that share clinical and pathological features. Clinically, TMA is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and end organ injury. Medications are important acquired cause of TMA, and they include Antiangiogenesis drugs, mitomycin-C, IFN, thienopyridine, quinine \((\text{George et al., 2014})\).

**Mesangial cell injury**, nodular glomerulosclerosis (NOS) has emerged as a specific lesion associated with cigarette smoking \((\text{Kuppachi et al., 2006})\).

**Drug-induced glomerular disease: Immune mediated injury**

Induced autoimmune disease was initially described decades ago, with reports of vasculitis and a lupus-like syndrome in patients taking
hydralazine, procainamide, and sulfadiazine. Over the years, multiple other agents have been linked to immune-mediated glomerular disease, often with associated autoantibody formation. Certain clinical and laboratory features may distinguish these entities from their idiopathic counterparts, and making this distinction is important in the diagnosis and management of these patients. Exposure to certain drugs can elicit an immune response that result in the generation of autoantibodies and clinical autoimmune disease, including immune complex or pauci immune GN. Awareness of these association by clinicians is important in discerning drug-associated syndromes from their primary counterparts, a distinction that may affect prognosis and treatment (Jonathan et al., 2015).

**ANCA-associated vasculitis (AAV),** reports emerged linking drugs to vasculitis. This hypothesis was strengthened after discovery of ANCAAs (anti-neutrophil cytoplasmic antibody) and their target antigens protienase 3 (PR3) and myeloperoxidase (MPO), also there are additional autoantibodies in patients with AAV e.g antibodies to elastase or lactoferrin. Drugs commonly implicated in ANCA-associated vasculitis involve cocaine, levamisole, hydralazine, antithyroid medicatios, minocycline, allopurinol, penillamine, and sulfasalazine (Almroth et al., 1992).

**Drug induced lupus (DIL),** the drugs most commonly associated with DIL were hydralazine and procainamide, with incidence as high as 5%-8% and 20% respectively, during the first year of therapy. There has been a reduction in DIL in parallel with decreased use of these agents.

DIL has only a minor increase in preponderance in women and tends to occur in older individuals compared with idiopathic systemic
lupus erythromatosus (SLE). Systemic symptoms, including fever, anorexia, weight loss, and arthralgia, are common. Skin manifestations (including macular, maculopapular, urticarial, or vasculitic rashes) are less common than in classic SLE. Although arthritis, serositis, and hepatosplenomegaly may occur, major organ involvement is rare. GN (glomerulonephritis) is uncommon but has been reported with hydralazine, sulfasalazine, (PTU) (propyelthiouracil), penicillamine, and anti-tumor necrosis factor (TNF) therapy (Xios et al., 2014).

Drug associated with membranous nephropathy (MN), involve gold salts used in treatment of rheumatoid arthritis (RA), captopril which seems to be the only ACE-I associated with development of nephrotic syndrome and in most cases, biobisy findings of MN, and NSAIDS-associated MN which its incidence is difficult to determine, and a stringent criterion for this diagnosis is a rapid remission after withdrawal of these agents (Hallet al., 1987).
Aim of work

This review will highlight the glomerular diseases induced by drugs.
Pathophysiology of drugs nephrotoxicity

The entire population is presently exposed to a number of different pharmacologic agents which are taken with no scientific justification and without any medical control and prescription. This causes a widespread toxicity. As most drugs are excreted by the kidney, it is reasonable to assume that the kidney itself could be a privileged target of their toxic actions (Bartoli, 2016).

Drugs nephrotoxicity can be caused through the entities discussed below.

1) Immunologic reactions caused by drugs involving the kidney:

A) Immune complex (IC) nephrotoxicity

In IC nephrotoxicity, drugs can be contained in IC, causing acute glomerulonephritis (AGN) or acute interstitial nephritis (AIN) usually secondary to a spillover mechanism: the excess IC which does not bind to glomerular structures “spills over” into the interstitial microcirculation, binding to tubular BM, triggering interstitial inflammation (Katz et al., 2010).

Drugs primarily affecting the immune system cause almost exclusively glomerular disease and, to a minor extent, interstitial disease. They trigger a lupus-like syndrome, reported with alpha-methyl-dopa, D-penicillamine, interferon, levamisole, procainamide and many other substances exerting blockade of immune recognition (Carlson et al., 2014).

B) hapten-mediated disease

In hapten-mediated disease (Haptens are epitopes represented by drugs). The immunologic reaction to haptens causes disease by the inflammatory effect of Ab-hapten interaction. This occurs mainly in the
renal interstitium, where haptens bind to tubular BMs or interstitial matrix, leading to AIN. The disease can subside after discontinuation of the offending agent, with prednisone treatment, or proceed to chronic interstitial nephritis ending in chronic renal failure (CRF) (Jahnukainen et al., 2013).

Known haptens include penicellins (esp. methicillin), cephalosporins, NSAIDS, hydrogen-ion pump inhibitors plus a number of miscellaneous other substances. In many circumstances, the reaction is IgE or IgG4 mediated, with eosinophils infiltrating the interstitium, attended by eosinophiluria: this is called “allergic” AIN, even though the Ag is not an “allergen (Magalhães-Costa et al., 2015).

Clinically, interstitial nephritis characterized by back pain caused by renal swelling. Urine output increases initially despite the fall in glomerular filtration rate (GFR) an important clue to the diagnosis. Sterile pyuria, low-grade proteinuria made up by “tubular” protein. Fever relapsing during antibiotic treatment after an initial resolution constitutes an additional clue and is more suggestive if associated with peripheral eosinophilia (González et al., 2008).

2) Analgesic nephropathy:

This is a chronic process which leads slowly over many years to CRF by causing an interstitial nephropathy. The toxic effect is dose related, and requires the continuous daily intake of analgesic for decades.

The increase in plasma creatinine (PCr) is slow and undetected for a long time. The disease can be suspected for an acute episode, like papillary necrosis or infection, or because of imaging that detects
shrunken kidneys with an irregular outline, distorted pelvis and papillary calcifications (Buckalew et al., 1986).

3) Direct toxic effects of drugs on the kidney:

AIN can be due to the direct toxic effects of pharmacologic agents on tubular epithelial cells. There is evidence indicating that the damaged tubular cell releases cytokines, activating T-cell-mediated immunologic responses that cause fibroblast activation, interstitial fibrosis and, consequently, CRF. This toxicity can lead to acute tubular necrosis (ATN), acute renal failure (ARF), rapidly progressive interstitial fibrosis ending in subacute renal failure and chronically progressive interstitial fibrosis ending in CRF (Pohl et al., 2011).

A) ATN can be produced by a number of offending drugs, such as clindamycin, antiviral agents, substances that precipitate as microcrystalline aggregates into the tubular lumen, and, X-ray contrast media. ARF is the clinical counterpart of ATN in most circumstances. PCr rises rapidly, the patient becomes oliguric up to total anuria (Xie et al., 2013).

The urine is isosthenuric, contains epithelial tubular casts, epithelial cells, leukocytes and leukocyte casts, scanty proteinuria, variable hematuria. The presence of muddy brown casts is typical, although it occurs also in rhabdomyolysis-induced renal failure. The anuric phase can progress to CRF directly, or recover variably, often completely (Xie et al., 2013).

B) Contrast ARF has become the most common type of drug induced renal failure. “True” contrast ARF is characterized by a typical onset: the morning following the exposure, the patient tells the
physician that he has not voided. Anuria or extreme oliguria last, on average, 5–7 days, during which PCr continues to rise to levels compatible with complete interruption of filtration. When the urine output resumes, it becomes polyuric, to subsequently return to normal together with PCr. Most authorities studying the disease define it as a rise in PCr > 25%, or an absolute change >0.5 mg/dL, beginning within 48 or, at most, 96 h after exposure (McCullough et al., 2006).

This entity is nowadays called contrast-induced nephropathy (CIN), as ARF with anuria is very rare, while a variable worsening of renal function is common. Several precautions are taken minimizing the risk of CIN including Use non-ionic hypo-osmolar contrast media, Provide the minimum volume of dye (less than 125 ml) and the less risky venous route rather than intra-arterial injections, if possible and Provide prophylaxis with saline infusion 1.5% of BW 6 h before and after the exam, adding 600 mg of N-acetylcysteine to the last bottle before and after contrast infusion (Davidson et al., 2006).

C) Gadolinium renal failure, executing nuclear magnetic resonance (NMR) with a gadolinium contrast in patients with preexisting renal failure has caused a high incidence of the so-called “nephrogenic systemic fibrosis” (NSF). Dialysis removes the toxic gadolinium compound (Zou et al., 2011).

4) Selective toxic effect of drugs on the kidney:

A) Cisplatin, iphosphamide and their congeners selectively damage tubular transport systems through intracellular hydroxyl radical formation. Polyuria and glycosuria occur initially; subsequently, oliguria occurs when renal failure worsens. Hypercalciuria, hyperphosphaturia and hypermagnesuria
occur due to selective impairment of calcium (Ca), phosphorus (PO4) and magnesium (Mg) transport systems, attended by their reduced serum concentrations (Jones et al., 1995).

B) Aminoglycoside antibiotics are cleared from the body exclusively through glomerular filtration, their clearance being equal to GFR. They exert concentration-dependent renal toxicity, which is maximal for colistin: the initial fall in GFR reduces their clearance, raising their plasma concentration: this begins a vicious circle that enhancing the toxic effect, initiates progression to ARF. The clinical picture is typical: the patient refers nocturia, heralding polyuria, due to the impairment of the countercurrent mechanism caused by interstitial edema and inflammation, plus nephrogenic diabetes insipidus (NDI). Polyuria is quickly followed by normoglycaemic glycosuria due to alteration of glucose transport. Initially, at the onset of polyuria and glycosuria, GFR is only slightly impaired, while it drops progressively with continuing administration of the antibiotic (Humes et al., 1982).

C) Amphotericin B displays a dose-related toxic effect characterized by rising creatinine, a short-lived polyuria followed by oliguric renal failure, renal tubular acidosis (RTA) and magnesium wasting. Liposomal preparations are well-tolerated because of slow release of the agent (White et al., 1998).

5) Herb medications:

Some of them cause renal failure, because of their content in aristolochic acid and tetrandrine, producing progressive and asymptomatic interstitial fibrosis and apoptosis of renal tubules, ending in
CRF. They are extremely dangerous as they run asymptomatically till renal failure is no longer reversible (Allard et al., 2013).

6) Hemodynamic mechanisms:

A) Cyclosporine A and congener drugs cause vasoconstriction and platelet aggregation, related micro-thrombotic disease and decreased nitric acid production-increased expression of transforming growth factor- beta (TGF-β). The toxicity is heralded by malignant, drug refractory hypertension, attributed to endothelin activation (Castello et al., 2005).

B) Oral contraceptives, by increasing renin substrate, they cause hypertension, which can progress into a malignant phase with mechanisms similar to those of cyclosporine A and thrombotic thrombocytopenic purpura (TTP), ending in end stage renal disease (ESRD) (Laragh et al., 1976).

C) PG (prostaglandin) inhibitors, aspirin and practically all NSAIDs can cause a renal hemodynamics-induced renal failure. Curiously, the angiotensin blockade in CRF and renal artery stenosis, where the peptide is maximally activated, can cause ARF by selectively lowering the resistance of the glomerular afferent arteriole (Cavarape et al., 2003).

7) Crystalline nephropathy:

This is due to intraluminal precipitation of the offending drugs e.g. Acyclovir i.v. causes a pure microcrystalline disease, which is prevented by volume expansion, Methotrexate and sulfadiazine precipitate at acid pH, an event prevented by HCO3 administration, Triamterene exerts toxic effects by microcrystalline disease, occasional AIN, and
Chapter I Pathophysiology of drugs nephrotoxicity

Sulfonamides can cause AIN which being cations, they reproduce the effects of amiloride and triamterene on the distal tubule, causing hyperkalemia, slight metabolic acidosis and distal RTA (Nasr et al., 2014).

8) Miscellaneous

Osmotic agents (dextran, mannitol and glycerol) are used to treat brain edema. ARF after massive administrations has been reported, denominated osmotic nephrosis. It is due to swelling of proximal tubule (PT) cells, with obstruction of the lumen and consequent fall in filtration rate (Dickenmann et al., 2008).

Lithium, used as an anti-depressant, determines NDI when it reaches toxic concentrations in plasma, usually above 1.5 mEq/L (Raedler et al., 2007).
Diagnosis and treatment:

Table (1): Methodology for establishing a link between a drug and an adverse event (Merkel, 2001).

<table>
<thead>
<tr>
<th>Methods to link specific drugs with an adverse drug reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Exclusion of other agents</td>
</tr>
<tr>
<td>(2) Withdrawal of culprit drug</td>
</tr>
<tr>
<td>(3) Rechallenge</td>
</tr>
<tr>
<td>(4) Singularity of drug (i.e., no other potential offending agent used)</td>
</tr>
<tr>
<td>(5) Consistent pattern of adverse drug reaction</td>
</tr>
<tr>
<td>(6) Quantitation of drug level (when possible/pertinent)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Degrees of certainty for causality of a drug-associated event</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Causative—ideally would involve a diagnostic test that is specific for a drug-associated event</td>
</tr>
<tr>
<td>(2) Probable—consistent with a drug event but lacking specific objective evidence for the link between drug and event</td>
</tr>
<tr>
<td>(3) Possible—the event can be neither confirmed nor excluded as an adverse drug event</td>
</tr>
<tr>
<td>(4) Coincidental—additional investigation reveals another cause of the event</td>
</tr>
<tr>
<td>(5) Negative—additional investigation excludes the association (e.g., drug never taken)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence for causality of a drug-associated event</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Excellent—prospective, controlled trials; large case-control series; animal models; large number of reports</td>
</tr>
<tr>
<td>(2) Good evidence—large case series; separate case reports with consistent pattern of disease and good quality</td>
</tr>
<tr>
<td>(3) Fair evidence—individual case reports of good quality</td>
</tr>
<tr>
<td>(4) Poor evidence—individual case reports of poor quality</td>
</tr>
</tbody>
</table>

When a physician recognizes a worsening of renal function, he should take a careful drug history and assess whether any of the drugs taken could be responsible for the renal impairment (Table 1). PCr and electrolyte concentrations must be measured, and their time change examined. Urinalysis should be performed invariably, as well as other exams when necessary, like acid–base status, enzymuria, renal echography, urine cultures, eosinophiluria and eosinophil blood count.
Analyzing and connecting the changes observed and the history taken, it is possible, on the grounds of the clinical-laboratory descriptions, to ascertain the likelihood of an adverse renal drug effect. In dubious circumstances, discontinuing the putative offending agent and instituting an appropriate steroid treatment can be a better option than performing a renal biopsy (merkel, 2001).
Drug induced glomerular disease: Direct cellular injury

Direct glomerular cellular injuries are stratified by the cell type at which the glomerular lesion is focused: visceral epithelial cell (or podocyte), endothelial cell injury and mesangial cell injury.

1) **Epithelial cell injury**:

The drug-induced podocytopathies consist of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), including both FSGS not otherwise specified (FSGS-NOS) and collapsing FSGS (C-FSGS). Multiple therapeutic agents are associated with both conditions (Table 2) (*Markowitz et al., 2010*).

**Table (2):** Medications associated with MCD and FSGS (*Markowitz et al., 2010*).

<table>
<thead>
<tr>
<th>Medications associated with minimal change disease and FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal change disease</strong></td>
</tr>
<tr>
<td>• IFN-α and –β</td>
</tr>
<tr>
<td>• Pamidronate</td>
</tr>
<tr>
<td>• Lithium</td>
</tr>
<tr>
<td>• Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>• Cyclooxygenase-2 inhibitors</td>
</tr>
<tr>
<td><strong>FSGS</strong></td>
</tr>
<tr>
<td>• IFN-α and –γ</td>
</tr>
<tr>
<td>• Pamidronate</td>
</tr>
<tr>
<td>• Lithium</td>
</tr>
<tr>
<td>• Sirolimus</td>
</tr>
<tr>
<td>• Anabolic steroids</td>
</tr>
<tr>
<td><strong>Collapsing FSGS</strong></td>
</tr>
<tr>
<td>• IFN-α, -β, and –γ</td>
</tr>
<tr>
<td>• Pamidronate (rarely zoledronate or alendronate)</td>
</tr>
<tr>
<td>• Anabolic steroids</td>
</tr>
</tbody>
</table>
A) Interferones (IFN)

The IFNs are types of cytokines that were initially known for their ability to interfere with viral replication. There are three main types of IFNs: α, β and λ. IFN-α is mainly synthesized by leukocytes (other than lymphocytes), IFN-β is mainly fibroblast derived, and IFN-λ originates from T cells and natural killer cells. IFN-α and β are mainly produced by virally infected cells, act through common receptors, and induce changes in neighboring cells that block viral replication. In contrast, IFN-λ acts to stimulate macrophage activation and major histocompatibility complex (MHC) expression. Collectively, the IFNs are a critical component of the innate immune system that protects against viral infection. IFNs are indicated for the treatment of multiple medical conditions. IFN-α is used in the treatment of hepatitis B and C and various malignancies. IFN-β is extensively used to treat multiple sclerosis. IFN-λ is indicated for chronic granulomatous disease and malignant osteopetrosis. All three forms are administered through the subcutaneous or intramuscular route and are associated with constitutional effects and laboratory abnormalities that limit their use (Markowitz et al., 2010).

Treatment with IFN has been associated with nephrotic syndrome with histologic findings of MCD, FSGS-NOS, or C-FSGS (Markowitz et al., 2010).

The exact mechanism of renal damage associated with IFN is currently unknown. IC glomerulonephritis due to interferon-anti-interferon IC is a theoretical consideration. Among the diverse speculations to explain the etiological role of interferon causing severe proteinuria, it is tempting to consider a sequence where IFN may participate in alteration of protein glomerular permeability either directly
or through release of other cytokines by activating T lymphocytes (Tovar et al., 2008).

In an experiment by Bino et al., crescentic glomerulonephritis was shown by injecting interferon to newborn mice. IgG, complement, and, in some places, IgM storage was demonstrated with the biopsy material obtained (Bino et al., 2004).

Individuals with genetic variants in the Apolipoprotein L1 (APOL1) gene have greatly increased risk of kidney disease. The high-risk genotypes are associated with elevated risk (7–29-fold) of FSGS, hypertension-associated end-stage renal disease. Only individuals with recent African ancestry carry these risk variants, explaining a large part of the 4-5-fold increased rate of kidney disease in African Americans compared with Caucasians (Dummer et al., 2015).

Nichols et al. reported a cohort of patients who developed C-FSGS while receiving therapeutic IFN (fig.1), all of whom carried the APOL1 high-risk genotype. This finding raised the possibility that IFN and the molecular pattern recognition that stimulate IFN production may contribute to APOL1-associated kidney disease. In cell culture, IFN and toll-like receptor agonists increased APOL1 expression up to 200-fold. PolyI: C, a double-stranded RNA TLR3 agonist, increased APOL1 expression by upregulating interferons directly or through an interferon-independent pathway with another pathway like NF- B and jak kinases. Although our patient is not African, FSGS developed after using IFN treatment (Nichols et al., 2015).

There is no proven treatment for renal toxicity associated with IFN. The common practice is to cease IFN and administer steroids. While renal functions recover following treatment discontinuation in some cases,
renal functions remain unchanged and even progress to ESRD in others. The factors involved in this process are yet unknown. Case-based evaluation indicates a relationship between renal functions and degree of collapse and sclerosis of the glomeruli and the presence of comorbidities including diabetes and hypertension (Harbi et al., 2014).

FSGS treatment is important, firstly excluding secondary causes that can lead to disease and determining the bad prognostic factors. While proteinuria amount is 0.5–2 g/day with conventional treatments, for nephrotic-range proteinuria, renal function impairment, and presence tubulointerstitial damage in biopsy aggressive treatment is recommended. Treatment options include blood pressure control, use the ACE inhibitors, statins, corticosteroids, cytotoxic drugs (cyclophosphamide and chlorambucil), calcineurin inhibitors (cyclosporine), mycophenolate mofetil, vitamin E, perflaxacin, plasmapheresis, and immunoadsorption (Pollak et al., 2008).
Figure 1: Pathologic findings. **(A)** A glomerulus with collapsing FSGS exhibits global wrinkling and retraction of the glomerular basement membranes and diffuse swelling and proliferation of overlying visceral epithelial cells (Jones methenamine silver). **(B)** In this glomerulus with collapsing FSGS, some of the podocytes are detached from the glomerular basement membrane and lie free within the urinary space (periodic acid Schiff). **(C)** On ultrastructural evaluation, visceral epithelial cells exhibit microvillous transformation and complete foot process effacement. An endothelial TRI is present. **(D)** At high magnification, an endothelial TRI is seen. Magnifications: ×400 in A and B; ×5000 in C; ×8000 in D (Nichols et al., 2015).
B) Bisphosphonates:

Bisphosphonates inhibit the differentiation of osteoclast precursors, induce apoptosis of osteoclasts, and stimulate the release of osteoclastic inhibitory factor from osteoblasts. Orally administered bisphosphonates are regularly used for the treatment of osteoporosis, whereas hypercalcemia and osteolytic metastases are mainly treated by intravenous administration of bisphosphonates (Polascik et al., 2005).

Two bisphosphonates are approved for this indication in the United States: pamidronate and zoledronic acid. Nephrotic syndrome has been reported after the use of pamidronate. In contrast, the main pattern of nephrotoxicity associated with zoledronic acid is ATN. The most common pattern of injury associated with pamidronate is C-FSGS (Perazella and Markowitz, 2008).

A toxic effect on the podocyte plays an important role in the pathogenesis of bisphosphonate related C-FSGS. It is suggested that bisphosphonates disrupt the cytoskeleton of the podocyte similar to their effect in osteoclasts. Additionally, mitochondrial toxicity can contribute to podocyte injury. This effect is mainly reported for bisphosphonates that contain amino groups (pamidronate, zolendronate, ibandronate, risedronate, alendronate) which are considered to be more effective than nonamino-bisphosphonates (etidronate, clodronate) (Sauter et al., 2006).

Other glomerular diseases such as minimal change nephropathy and the classical variant of FSGS have also been linked to bisphosphonate treatment although this is reported less frequently (Barri et al., 2004).

Finally, the use of bisphosphonates has also been associated with acute kidney failure, related to a direct toxic effect on the tubular
Chapter II  
Drug induced glomerular disease: Direct cellular injury

epithelium causing acute proximal tubular necrosis or tubulointerstitial inflammation \( (\text{Smetana et al., 2004}) \).

The association between the use of i.v. pamidronate and the development of C-FSGS was first described by Markowitz in a group of 7 patients. Six of these patients received pamidronate because of multiple myeloma and one patient because of bone metastases of breast cancer. Pamidronate was given over a period of 15 to 48 months in monthly doses varying from 60 to 360 mg. All patients had a normal kidney function at the start of pamidronate treatment but developed nephrotic syndrome during the treatment. At the time of the kidney biopsy disclosing FSGS, mean proteinuria amounted to 12.4 g per day and the mean serum creatinine concentration was 317\( \text{lmol/l} \). Four patients required hemodialysis therapy. In three of the five patients in whom pamidronate treatment was discontinued, renal replacement therapy could be avoided, although the nephrotic syndrome persisted. Two of these three patients were also treated with steroids. The temporal relationship between the use of pamidronate and the development of C-FSGS was confirmed by several case reports \( (\text{Markowitz et al., 2001}) \).

Although many patients recovered after withdrawal of pamidronate, some patients have remained dependent on renal replacement therapy. In one of the reported cases a relapse of the nephrotic syndrome occurred after restarting pamidronate. Occasionally, C-FSGS has been reported in association with the use of other bisphosphonates, i.e., oral alendronate and i.v. zolendronate \( (\text{Nagahama et al., 2009}) \).

The incidence of C-FSGS or proteinuria as a result of bisphosphonate treatment is unclear, since the reported cases have not been related to the number of patients at risk. Although most cases have been
described in association with the use of pamidronate, the occurrence of C-FSGS during treatment with alendronate and zolendronate suggests that it is a class effect. More quantitative data are available on the risk of kidney failure due to bisphosphonate therapy. In two cohorts comprising nearly 2100 patients with multiple myeloma or bone metastases of solid tumors, renal failure was found in about 10% of the patients that received repeated i.v. infusions of pamidronate or zolendronate (*Dermott et al., 2006*).

The risk of renal failure following zolendronate therapy was not significantly different from that following pamidronate therapy. Ibandronate was less nephrotoxic compared to zolendronate. This difference may be explained by differences in pharmacokinetics: compared to zolendronate and pamidronate, ibandronate is more highly protein bound (87% vs. 56 and 54%). This may limit renal exposure to free drug. Moreover, the renal tissue half-life of ibandronate is much shorter than that of zolendronate, possibly allowing for more time for injured cells to recover in between repeated dosing (*Diel et al., 2009*).

Based on the data regarding risk factors for nephrotoxicity, the American Society of Oncology has formulated dosing guidelines for the use of intravenous bisphosphonates. For zolendronate, it is recommended to reduce the dose in patients with an estimated GFR between 30 and 60 ml/min. In this population, no changes in infusion time or interval are required. Zolendronate is not recommended for use in patients with an estimated GFR below 30 ml/min as its safety has not been tested in this group. In patients with an estimated GFR below 30 ml/min who are treated with pamidronate, it is recommended to extend the infusion time from 4 to 6 h and to consider dose reduction. During long-term bisphosphonate therapy, it is recommended to monitor serum
creatinine concentration and urinary protein excretion every 3–6 months. When albuminuria exceeds 0.5 g/day or serum creatinine rises, therapy should be withheld until the renal problems are solved. In patients with an estimated GFR below 30 ml/min, ibandronate may be a better choice; however, further studies are required to confirm its safety (American Society of Clinical Oncology, 2007).

In contrast to I.V. administration, oral treatment with bisphosphonates has not been associated with kidney failure. In a pooled analysis of nine clinical trials including 8996 postmenopausal women with osteoporosis and renal insufficiency, treatment with risedronate at a daily dose of 5mg during three years did not increase the risk of additional renal impairment when compared to placebo (Miller et al., 2005).

C) Lithium:

Lithium, the lightest alkyl metal, is commonly employed in the treatment of bipolar psychiatric disorders. The more commonly reported adverse renal effects during lithium therapy are renal tubular acidosis, nephrogenic diabetes insipidus, and chronic interstitial nephritis. An uncommon side effect is lithium-induced nephrotic syndrome. Mild proteinuria is a common finding after 2 years of lithium therapy. However, the nephrotic syndrome is a rare, idiosyncratic effect of lithium carbonate (Bosquet et al., 1997).

Possible pathophysiological links between minimal change disease and lithium have been proposed. It has been suggested that minimal change disease is a disorder of cell-mediated immunity resulting in the production of a circulating lymphokine toxic to the podocytes. Lithium has been proposed to modulate the T cell-dependent immune system. Wu and Yang demonstrated that lithium enhances interleukin-2 (IL-2)
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production in human T cells. Lithium also augments the IL-1-induced synthesis of IL-6, GM-CSF (graulocyte-macrophage colony stimulating factor), IL-3, and IL-2 in murine T cell hybridoma cells. In the same model, lithium modulates both tumor necrosis factor (TNF)-mediated cytotoxicity and TNF induced and IL-1-induced cytokine expression. T cell stimulation requires the activation of both the phosphoinositol pathway as second messenger systems. Lithium is a well-known activator of the phosphoinositol pathway. Tam et al., showed that osteoblastic cells, when preincubated with lithium, showed an amplified response to different stimulators, such as endothelin-1 (Tam et al., 1996).

There have been only 20 reported cases of nephrotic syndrome associated with the use of lithium. In adult, MCD is the most common pathology seen with lithium-associated nephrotic syndrome. However FSGS has been described in a few cases. Proteinuria generally begins 1.5–10 months after starting lithium therapy (Bosquet et al., 1997).

In MCD, the proteinuria usually resolves 1–4 weeks after discontinuation of the lithium. However, some cases have required treatment with corticosteroids. In several patients, reinstitution of lithium led to recurrence of the nephrotic-range proteinuria, strongly suggesting an etiological role for lithium (Bosquet et al., 1997). The relationship with FSGS is less clear. In some cases, cessation of the lithium did not lead to resolution of the nephrosis, suggesting the patient had either primary FSGS or a secondary FSGS due to tubulointerstitial disease. However, in other cases, as in our report, the proteinuria resolved after discontinuing the lithium. If lithium therapy is to be continued long term, renal function (i.e., creatinine) should be monitored every 3–6 months, as 15%–20% of patients on chronic lithium
therapy develop a slowly progressive decrease in GFR. Although GFR rarely falls below 40–60 ml/min, cases of ESRD secondary to lithium have been described. The greatest risk of this outcome is having a serum creatinine greater than 2.5 mg/dl at the time of biopsy. It has been recommended that if the serum creatinine exceeds 2.0 mg/dl, lithium therapy should be discontinued permanently, given the increased risk of ESRD (Markowitz et al., 2000).

D) NSAIDS:

NSAIDs are a broad class of medications with analgesic, antipyretic, and anti-inflammatory properties. These widely used agents inhibit cyclooxygenase-1 (COX-1) and COX-2, thereby blocking prostaglandin, prostacyclin, and thromboxane production. NSAIDs are associated with multiple patterns of nephrotoxicity, including hemodynamically-mediated ATN, AIN, MCD, papillary necrosis, and, rarely, membranous nephropathy. NSAID-associated MCD was first reported in three patients with AKI and NS who had biopsy findings of both AIN and MCD that remitted after NSAID discontinuation. A subsequent literature review noted that NSAID-associated MCD may occur in the absence of AIN. This report included 24 patients with MCD, among whom 15 patients received fenoprofen. Patients presented with full-blown NS and had excellent outcomes after NSAID discontinuation, often in the absence of corticosteroids (Feinfeld et al., 1984).

NSAIDs subsequently have been recognized as a drug-induced etiology of MCD. Unlike IFN, lithium, and bisphosphonates, which are associated with MCD and FSGS, available data do not support a relationship between NSAIDs and FSGS. The observation that MCD occurs with multiple classes of NSAIDs with distinct chemical structures
suggests that the pathogenesis of MCD and other NSAID-associated nephropathies may involve shunting of AA (amino acid) metabolites into alternative pathways that modify immune function. Of note, the COX-2 inhibitors, a newer class of NSAIDs that selectively inhibits COX-2, have also been associated rarely with MCD. Although drug discontinuation is often associated with remission of MCD, a course of steroids may be beneficial when NS persists despite drug withdrawal \( (Alper \ et \ al., \ 2002) \).

\[ E) \ \textbf{Additional therapeutic agents associated with FSGS:} \]

Treatment of recipients of renal transplants with sirolimus, a mammalian target of rapamycin inhibitor, commonly accompanied by an increase in proteinuria, which is usually subnephrotic \( (Murakami \ et \ al., \ 2014) \).

C-FSGS and FSGS-NOS have been reported in bodybuilders after long-term anabolic steroid use. In 2010, Herlitz et al. described 10 patients with mean urine protein of 10.1 g/d and serum creatinine of 3.0 mg/dl, including three patients with classic nephrotic syndrome. In seven patients with available followup who discontinued anabolic steroid use, stabilization or improvement in proteinuria and kidney function was noted. Rechallenge in one patient led to rapid worsening of proteinuria and renal dysfunction. The pathogenesis may involve hyperfiltration in response to increased (lean) body mass as well as direct nephrotoxic effects of anabolic steroids \( (Herlitz \ et \ al., \ 2010) \).
2) Endothelia cell injury

Thrombotic microangiopathy (TMA) is a term that has been applied to multiple seemingly unrelated conditions that share clinical and pathologic features. Clinically, TMA is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and end organ injury. Pathologic findings in TMA target the endothelial cell and include endothelial swelling and necrosis, glomerular and vascular thrombosis, mesangiolysis, glomerular basement membrane duplication with cellular interposition, mucoid intimal edema, and fibrin deposition (fig. 2) (George and Nester, 2014).

Conditions associated with TMA include hereditary and acquired disorders and may present acutely with catastrophic effects or gradually with chronic end organ injury (Shenkman and Einav, 2014).
Figure (2): Drug induced TMA. (A) A glomerulus from a patient treated with gemcitabine exhibits subacute findings of thrombotic microangiopathy, including global double contours of the glomerular basement membrane (tram tracking), cellular interposition, and dissolution of the mesangial matrix consistent with mesangiolysis. Mild swelling of endothelial and visceral epithelial cells is also noted. Jones methenamine silver, 3600. (B) A glomerulus from the same patient exhibits a fresh fibrin thrombus in a preglomerular arteriole. Hematoxylin and eosin, 3600. TMA, thrombotic microangiopathy (George and Nester, 2014).
Medications are an important acquired cause of TMA and examples are showed in the following table (Table 3).

**Table 3**: Drugs reported to have a definite association with TMA ([Zayd et al., 2015](#))

<table>
<thead>
<tr>
<th>Drug</th>
<th>Immune Definite evidence</th>
<th>Immune Probable evidence</th>
<th>Toxic Definite evidence</th>
<th>Toxic Probable evidence</th>
<th>No. of patients reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cocaine</td>
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</tr>
<tr>
<td>Cyclosporine</td>
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<td>15</td>
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</tr>
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<tr>
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<tr>
<td>Gemcitabine</td>
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<tr>
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<tr>
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<td>1</td>
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<tr>
<td>polycarbadoxylate</td>
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<tr>
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<tr>
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<tr>
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</table>
A) Antiangiogenesis Drugs

Antiangiogenesis drugs (AADs) are used to treat a number of cancers as well as various neovascular eye disorders. AADs include monoclonal antivascular endothelial growth factor (anti-VEGF) antibodies (bevacizumab), circulating VEGF decoy-receptor molecule (aflibercept), and VEGF receptor tyrosine-kinase inhibitors (sunitinib, sorafenib, axitinib, and pazopanib). Their anticancer efficacy is on the basis of observations that many malignancies proliferate and disseminate by promoting unregulated tumor angiogenesis through dysregulation of the VEGF signaling pathway. Antiangiogenesis is also effective in nonmalignant neovascular processes, where nephrotoxicity is a rare occurrence (Gurevich and Perazella, 2009).

AKI is seen. This pattern of renal injury, which is more common with anti-VEGF antibodies or decoy receptor therapy than with tyrosine-kinase inhibitors, has been described in over 100 patients (Izzedine et al., 2014).

These drugs produce a clinical-pathologic picture quite similar to preeclampsia, which is driven, in part, by a similar molecular mechanism. MAHA and thrombocytopenia are only observed in approximately 50% of patients, despite the findings of acute or chronic TMA in the kidney. Hypertension (HTN) occurs in 80% of patients, whereas proteinuria is nearly universal and ranges from low grade to nephrotic range. Urine sediment can be active with cylinduria and cellular/granular casts or bland. Kidney function ranges from mild injury to severe acute kidney injury (AKI) requiring dialysis. blood pressure (BP) control and drug withdrawal can be associated with return of kidney function, which is
relatively uncommon for TMA associated with others agents (Izzedine et al., 2014).

Interestingly, adverse renal effects often correlate with effective antitumor activity. Thus, nephrologists and oncologists have to balance drug withdrawal for nephrotoxicity against effective cancer therapy. We suggest that HTN and proteinuria should prompt antihypertensive therapy, whereas AKI is an indication to interrupt drug therapy (Rini et al., 2011).

B) Chemotherapeutic Agents

✓ Mitomycin-C:

Mitomycin-C is an alkylating agent used to treat various malignancies. After the recognition of the association between mitomycin-C therapy and TMA, a registry identified 85 patients, and subsequent clinical trials noted a TMA incidence ranging from 4% to 15%. Kidney injury is dose dependent, with a cumulative dose .60 mg significantly increasing TMA risk. The mechanism is unknown, but direct toxic endothelial injury is favored over an immune-mediated process involving ADAMTS-13 or the alternative complement pathway. Although TMA can develop during drug exposure, it more often develops weeks to months after the last dose (mean of 75 days) (Zakarija and Bennett, 2005).

AKI is a defining feature of mitomycin-C–associated TMA and is often severe; one third of 85 registry patients required dialysis. Renal recovery can occur, but most patients are left with CKD. Systemic manifestations of MAHA and thrombocytopenia are common, whereas neurologic symptoms are rare (16%) (Zakarija and Bennett, 2005).
Treatment rests primarily on drug withdrawal, because steroids, plasma exchange/pheresis (PE/PH), and anticoagulation are generally ineffective. TMA-related mortality is approximately 44% (Zakarija and Bennett, 2005).

**Gemcitabine:**

Gemcitabine is a cell cycle–specific pyrimidine antagonist that is used to treat a variety of malignancies. TMA was described as a complication within a few years following approval, with an incidence ranging from 0.015% to 2.4%. Higher cumulative dose and prior exposure to other chemotherapeutic agents increase the risk for TMA. Drug-induced endothelial injury is the probable mechanism. Disruption of endothelial integrity may cause release of vWF (von willebrand factor) multimers and plasminogen activator inhibitor, reduce synthesis of prostacyclin and tissue plasminogen activator, and expose a denuded endothelial surface that favors platelet adhesion, leading to fibrin and platelet deposition in the renal microvasculature. TMA most often develops weeks to months after initiating gemcitabine therapy (Izzedine et al., 2006).

AKI is present in virtually all cases. In a case series of 29 patients with gemcitabine-associated TMA, all patients had MAHA, thrombocytopenia, and AKI, whereas new or worsening HTN, proteinuria, and hematuria were noted in 26 of 29 patients. Drug discontinuation or future avoidance resulted in full (n=58) or partial (n=511) recovery with CKD in three patients and ESRD in seven patients (25%). PE/PH had minimal or no effect. Reported mortality is wide-ranging (0%–90%), with 15% a reasonable estimate for TMA-specific death (Glezerman et al., 2009).
C) IFN

In addition to their association with MCD and FSGS, the IFNs are associated with the development of TMA. Over 30 patients with IFNα associated TMA have been reported, most often in the setting of chronic myelogenous leukemia. High-dose and prolonged regimens are most often associated with TMA (Deutsch et al., 2007).

Patients present with HTN, severe AKI often requiring dialysis, proteinuria, and active urine sediment, whereas MAHA and thrombocytopenia are variably present. In the patients reviewed, treatment included drug discontinuation and BP control, whereas PE/PH was performed in approximately two thirds of patients; antiplatelet agents and steroids were occasionally used. CKD and ESRD requiring dialysis are fairly common—nearly one half of patients reported developed long-standing kidney disease. Mortality occurs from TMA, but most deaths are caused by underlying malignancy (Hunt et al., 2014).

IFN-β causes TMA less commonly than IFN-α, with experience limited to a small number of cases and regulatory reports of patients with relapsing multiple sclerosis. Clinical features, treatment, and outcomes are similar to those described with IFN-α. The mechanism of IFN-associated TMA remains unclear, although three reports describe ADAMTS-13 autoantibody/deficiency (Orvain et al., 2014).

D) Thienopyridines

Ticlopidine, clopidogrel, and prasugrel are antiplatelet agents that target the P2Y12ADP receptor, and they are used to prevent and/or treat cerebrovascular accidents and coronary artery events, including stent
thrombosis. Paradoxically, this class of drugs is one of the most commonly implicated in drug-induced TMA (Jacob et al., 2012).

Ticlopidine was Food and Drug Administration (FDA) approved in 1991, and a case series subsequently described 60 patients with TMA. The incidence of TMA is approximately 0.02%, with the syndrome developing 2–12 weeks after drug exposure. Neurologic complications (72%) of TMA dominate, with AKI noted to be less severe and uncommon (29%). MAHA and thrombocytopenia are often present and can be severe (Zakarija et al., 2009).

In contrast to direct endothelial injury, ticlopidine appears to cause TMA through reducing ADAMTS-13 activity. Production of an inhibiting autoantibody is described, although how ticlopidine induces this effect is unknown. Molecular mimicry and hapten formation have been suggested. Interestingly, concomitant complement factor H mutations and ADAMTS-13 deficiency were described in four patients with ticlopidine-induced TMA, suggesting that two hits may be required in some patients (Chapin et al., 2013).

Although discontinuation of ticlopidine is required in patients with TMA, PE/PH provided added benefit, presumably by removing autoantibodies that promote thrombosis. Patients treated with PE/PH more commonly recover and have lower mortality rates (0%–40%) compared with drug discontinuation alone (50%–67%). CKD is an uncommon complication (Zakarija et al., 2009).

Clopidogrel entered clinical practice as an antiplatelet agent in 1998 driven by clinical trials showing better safety (no TMA in 20,000 patients) than ticlopidine. Currently, in part because of its sheer volume of use, clopidogrel has become the leading cause of drug-induced TMA.
As of 2011, the FDA received 197 reports of clopidogrel associated TMA, with an incidence that approximates 0.012\% (Zakarija et al., 2009).

In contrast to ticlopidine, TMA develops more rapidly, often within 2 weeks of exposure. AKI is more common (55\%) and typically more severe, whereas thrombocytopenia is mild. Interestingly, most cases are not explained by ADAMTS-13 deficiency/inhibitor, favoring direct drug-induced endothelial injury, enhanced release of ultralarge vWF, or an unknown mechanism. In addition to drug discontinuation, PE/PH has been used but seems to require prolonged treatment periods (3 weeks) for response in contrast to the 3–5 days required for ticlopidine-associated TMA. Recovery is common, but CKD is an established complication. Mortality from clopidogrel-associated TMA with and without PE/PH therapy is reported to be 28\% and 33\%, respectively (Jacob et al., 2012).

**Prasugrel** was FDA approved in 2009 for coronary stent thrombosis prevention, and as of 2011, 14 patients with TMA have been reported to the FDA. Notably, no TMA cases were described in clinical trials containing 1769 patients treated with prasugrel. As with clopidogrel, TMA generally develops within 2 weeks of exposure. Drug discontinuation and PE/PH are currently recommended (Jacob et al., 2012).

**E) Quinine**

Quinine has been used to treat muscle cramps and malaria, and despite an FDA ban on over-the-counter marketing, it remains widely available by prescription, in beverages and nutrition/health store products, and on internet sites. Although well recognized as a cause of immune thrombocytopenia, quinine is also an important cause of TMA. Quinine-
induced TMA is often characterized by oliguric or anuric AKI, frequently requiring dialysis (up to 85%), and laboratory manifestations of MAHA with severe thrombocytopenia (Izzedine et al., 2010).

The rapid development of TMA after a single quinine tablet bespeaks an immune-mediated process. Quinine-dependent IgG antibodies drive this process by binding to a broad range of cells, including platelets, white blood cells, and endothelial cells. Both antibody-induced endothelial injury and platelet activation may underlie the development of TMA. Quinine is not associated with ADAMTS-13 autoantibody or deficiency (Izzedine et al., 2010).

Drug discontinuation and plasmapheresis are indicated to remove the culprit antibody. Existing literature suggests that ESRD and CKD develop commonly (approximately 50%) after TMA, with a mortality of 21% in one large series. Relapse may occur with re-exposure (Park et al., 2009).

3) Mesangial cell injury:

Nodular glomerulosclerosis (NGS) has emerged as a specific glomerular lesion associated with cigarette smoking. The finding of nodular mesangial sclerosis with glomerular and tubular basement thickening, in the absence of immune deposits, is the classic description of nodular diabetic glomerulosclerosis. However, this same pattern of NGS (Figure 3) has been reported in patients without clinical evidence of diabetes (Herzenberg et al., 1999).
Figure 3: Nodular glomerulosclerosis of smoking. Pathologic findings in smoking-associated nodular glomerulus resemble changes seen in nodular diabetic glomerulosclerosis and include nodular mesangial sclerosis with thickening of glomerular and tubular basement membranes. Periodic acid–Schiff, 3500 (Herzenberg et al., 1999).

The lesion was first reported as “diabetic glomerulosclerosis without diabetes” and subsequently rebranded “idiopathic nodular mesangial sclerosis” or “idiopathic nodular glomerulosclerosis” (Herzenberg et al., 1999).

However, the publication of the first substantial case series on this entity in 2002, which included 23 patients compared with a total of 20 patients previously reported over 31 years and 13 publication, presented strong evidence that heavy cigarette smoking was linked to this lesion; 21 of 23 patients (91%) reported a history of tobacco use, with a mean
cumulative smoking history of 52.9 pack-years, and more than one half of patients were still smoking at the time of biopsy (Kuppachi et al., 2006).

A more recent series detailed 15 patients with idiopathic NGS over a 10-year period. Ten patients reported a history of smoking (mean cumulative smoking history of 54.2 packyears), and all were actively smoking at the time of biopsy (LiW and Verani, 2008).

It has been proposed that this distinct clinicopathologic entity should more appropriately be called “smoking-associated nodular glomerulosclerosis” (Nasr and Agati, 2007).

Tobacco-induced formation of advanced glycation end products (AGEs) may be a mechanism of injury in this form of NGS. AGE through interaction with receptor to AGE activates signaling cascades that promote mesangial cell synthesis of profibrogenic cytokines, including platelet–derived growth factor (PDGF) and TGF-β (Ceram et al., 1997).

Reactive glycation products, present in extracts of tobacco and tobacco smoke, can react rapidly with proteins to form AGEs, and increased levels of AGE have been found in the lenses and blood vessels of smokers (Nicholl et al., 1998).

Most patients with smoking-associated NGS present with evidence of renal dysfunction (mean creatinine .2.0 mg/dl) and nephrotic-range proteinuria. Predictably, given this clinical presentation, prognosis is generally poor, with a high likelihood of progression to ESRD. Smoking cessation may be an important intervention in modifying this natural history. In one series with .2 years follow-up postbiopsy, none of the patients who had discontinued smoking reached ESRD, whereas all of the patients who continued to smoke reached ESRD over a median time of 11 months (LiW and Verani., 2008).
Drug-induced glomerular Disease: Immune-mediated injury

Exposure to certain drugs can elicit an immune response that results in the generation of autoantibodies and clinical autoimmune disease, including immune complex or pauci-immune GN. Awareness of these associations by clinicians is important in discerning drug-associated syndromes from their primary counterparts, a distinction that may affect prognosis and treatment (Jonathan et al., 2015).

Here, we review drug-induced ANCA associated vasculitis (AAV), drug induced lupus (DIL), and drug associated membranous nephropathy (MN).

Drug-induced AAV:

ANCA vasculitides are small-vessel vasculitides that include granulomatosis with polyangiitis (GPA; formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome). Renal-limited ANCA-associated vasculitis can be considered the fourth entity in this group, although it eventually corresponds to a kidney-limited form of MPA or GPA in practice. Despite the rarity and still unknown cause(s) of ANCA-associated vasculitides, research pertaining to these diseases has been very active and steadily increasing over the past three decades. The results of several clinical and more basic fundamental studies demonstrated that each of these diseases has some different pathogenic mechanisms and genetic associations (Craven et al., 2013).
Terminology and Molecular Biology of ANCA.

The classical terms C-ANCA and P-ANCA describe IF (immunofluorescence) patterns on granulocyte substrates (fig.4). C-ANCA is largely due to the presence of autoantibodies targeting the serine protease proteinase-3 (PR3), while P-ANC is caused by antibodies directed mainly against myeloperoxidase (MPO) (Jennette et al., 1989).

Additionally, ANA and antibodies against the cytoplasmic granule antigens lactoferrin, lysozyme, azurocidin, elastase, cathepsin G, bactericidal/permeability-increasing enzyme (BPI) show the so-called atypical ANCA pattern on ethanol-fixed neutrophils. MPO is the most frequently recognized antigen in P-ANCA and primary systemic vasculitis (Radice et al., 2013).

PR3 is a weak cationic protein of 29-30 kDa molecular weight, belonging to the trypsin family of serine proteases. PR3 is synthesized as a preproenzyme and subsequently processed in four steps into the mature form. It is stored in the azurophilic granules of neutrophils but can also be found within the membrane of secretory vesicles. PR3 is physiologically inhibited by α1-antitrypsin (Radice et al., 2007).

MPO, which represents about 5% of the total protein content of neutrophils. The enzyme is characterized by a powerful bactericidal activity, whose peroxidase activity is physiologically inhibited by ceruloplasmin (Kallenberg et al., 2007).
Figure 4: Appearance of cytoplasmic indirect immunofluorescence pattern (C-ANCA, Figure 9(a) and perinuclear (P-ANCA, Figure 9(b) on ethanol-fixed human neutrophil cells (Radice et al., 2013).
**Drug induced AAV:**

Below in table 4 a list of drugs described to be associated with ANCA-associated vasculitis.

**Table 4:** Drugs commonly implicated in ANCA-associated vasculitis *(McGrath et al., 2011).*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence</th>
<th>Renal Involvement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine and levamisole</td>
<td>Multiple case series and case reports</td>
<td>44%(^a)</td>
<td>Skin manifestations in 61%(^a) Neutropenia in 28%(^a)</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Case series and case reports</td>
<td>80%–90%(^b)</td>
<td>Combined pulmonary-renal syndrome is rare (15 patients to date) Lupus-like syndrome is common</td>
</tr>
<tr>
<td>Antithyroid medications</td>
<td>PTU: multiple case series and case reports</td>
<td>May be common</td>
<td>Animal models also support association with PTU</td>
</tr>
<tr>
<td></td>
<td>Carbimazole and methimazole: case reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>Small case series and case reports</td>
<td>No reported cases of renal involvement with small-vessel vasculitis PAN with p-ANCA positivity and renal involvement reported</td>
<td>Conflicting data on ANCA seroconversion with minocycline use</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Case reports</td>
<td>Reported</td>
<td>Pulmonary-renal syndrome rarely reported</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Case reports</td>
<td>Reported</td>
<td>No seroconversion noted in analysis of scleroderma trial</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Case reports</td>
<td>Reported</td>
<td>Pulmonary-renal syndrome also reported No seroconversion noted in analysis of the CSSRD Trial</td>
</tr>
</tbody>
</table>

PTU, propylthiouracil; PAN, polyarteritis nodosa; p-ANCA, perinuclear ANCA; CSSRD, Cooperative Systematic Studies of the Rheumatic Diseases. \(^a\)Data from the largest case series of cocaine- and levamisole-associated, ANCA-associated vasculitis. \(^b\)Data from the largest series of hydralazine-associated, ANCA-associated vasculitis.
A) Cocaine- and Levamisole-Associated Vasculitis:

Multiple reports describe the development of vasculitis in cocaine users, including cutaneous vasculitis, cerebral vasculitis. Recently, the adulterant levamisole has been implicated as a culprit in cocaine-associated AAV (fig.5) (Merkel et al., 1995).

Levamisole has been used in humans for pediatric nephrotic syndrome, colon cancer, inflammatory bowel disease (IBD), and rheumatoid arthritis (RA). Reports exist describing cutaneous vasculitis and the presence of autoantibodies, including ANCAs, in patients exposed to levamisole (Wolford et al., 2012).

Levamisole has been detected with increased frequency in the illicit cocaine supply entering the United States and Europe over the last decade, with a 2011 Drug Enforcement Agency report noting contamination in 82% of the United States supply. Levamisole shares similar physical properties (appearance, smell, and taste) with cocaine, and it may mimic or potentiate the euphoric effects of cocaine through sympathetic nervous system stimulation (UNODC, 2011).

In 2009, cases emerged of cocaine users who presented with agranulocytosis followed by AAV with characteristic skin findings of small- (palpable purpura) and medium-vessel (retiform purpura vasculitis (Zhu et al., 2009).

McGrath et al. describe the largest case series of levamisole-associated AAV. Of 327 patients with newly positive ANCA titers between 2009 and 2010, 30 had evidence of active cocaine use by report or toxicology. On presentation, 83% had arthralgias, 61% had skin manifestations, 44% had ear/nose/throat involvement, 44% had evidence of renal involvement (defined by abnormal urine dipstick or urine
microscopy), 28% were neutropenic, and 17% had pulmonary hemorrhage. No patient had pulmonary renal syndrome. Two patients had severe AKI, one of whom underwent a kidney biopsy showing pauci-immune crescentic GN. Both of these patients were left with significant renal impairment, despite immunosuppression. Serologically, all patients were anti-MPO positive, and one half were anti-PR3 ANCA positive (McGrath et al., 2011).

Consistent with earlier observations in drug-associated AAV, patients with cocaine-associated AAV had higher anti-MPO levels (15 times) than patients with idiopathic AAV over the same period (range 51075–7988 versus median 5112; P,0.01), and many patients had additional abnormal serologies (ANA positive, 14 of 17; low C3 and/or C4, seven of 11; anti-dsDNA antibody positive, three of nine; positive lupus anticoagulant, six of nine). During the same time period, 15 of 21 new patients with AAV that were dual-ANCA positive (anti-PR3 and anti-MPO) were attributed to cocaine (Choi et al., 2000).

The mechanism of levamisole-associated AAV is unclear. HLA B27 positivity has been shown to increase the risk of levamisole-associated agranulocytosis, but its association with AAV has not been explored (Hodinka et al., 2000).

Treatment has focused on cessation of cocaine use and the use of immunosuppression in severe cases. However, cocaine’s widespread use and addictive nature present a unique challenge. Health care providers should have a high level of suspicion for cocaine/levamisole AAV in patients with high-titer anti-MPO ANCA, coexistent MPO and PR3 ANCA, other autoimmune serologies, leukopenia, severe cutaneous lesions, and recurrent AAV episodes (McGrath et al., 2011).
Figure 5: A glomerulus from a patient who used cocaine contained levamisole and presented with rapidly progressive GN and high-titer anti-myeloperoxidase ANCA. The glomerulus exhibits fibrinoid necrosis, multifocal rupture of the glomerular basement membrane, and an overlying, circumferential cellular crescent. Jones methenamine silver, 3400 (McGrath et al., 2011).

B) Antithyroid Drugs

Reports emerged in the 1990s of AAV, some with crescentic/pauci-immune glomerulonephritis (GN), in patients treated with propylthiouracil (PTU), carbimazole, and/or methimazole for hyperthyroidism (Kawachi et al., 1995).

Gunton et al. then explored the link between antithyroid drugs and ANCAs, finding that only one of 10 newly diagnosed patients developed ANCAs (atypical cytoplasmic ANCA and high anti-MPO titer) 8 months
after starting carbimazole in contrast to eight of 30 (27%) long-term patients. Patients who were ANCA positive were mostly p-ANCA/anti-MPO antibody positive, on PTU (seven of eight), and had a longer mean drug exposure (8.9 versus 2.8 years). Four of these patients had possible vasculitis symptoms that resolved after stopping the medications, although renal disease was not specifically mentioned. Five of eight patients became ANCA negative within 6 months of stopping antithyroid therapy. Gunton et al. concluded that ANCA positivity associated with long-term use of antithyroid medications (Gunton et al., 2000).

A cross-sectional analysis of 207 patients with hyperthyroidism in The Netherlands found that exposure to antithyroid medication (PTU, methimazole, and carbimazole) was associated with an 11.8 times higher odds (95% confidence interval, 1.5 to 93.3) of developing a positive ANCA serology (p-ANCA, cytoplasmic ANCA, or atypical p-ANCA on immunofluorescence or ELISA positive for anti-MPO, PR3, or human lactoferrin antibody) versus non exposure. Four of 13 patients with positive ANCA serologies had clinical signs or symptoms of vasculitis, three of whom had kidney biopsies showing necrotizing and crescentic GN. However, the association between antithyroid medications and development of a positive ANCA serology was no longer observed when patients with only anti–human lactoferrin antibody (a nonpathogenic ANCA) were excluded, and ANCA positivity was not related to any individual antithyroid drug or treatment duration (Slot et al., 2005).

A second study by Afeltra et al. detected a positive ANCA in 29% (six of 21) of patients with Graves Disease not being treated with PTU versus 9% (one of 11) of patients with Hashimotos thyroiditis and zero of 20 controls (Afeltra et al., 1998).
These two studies support the hypothesis that the risk for a positive ANCA serology may be linked to underlying autoimmunity rather than drug exposure.

The pathogenesis of drug AAV with these medications is poorly understood. One study showed a higher reactivity of sera in patients with PTU AAV against specific MPO fragments versus both patients with idiopathic AAV and patients with PTU-associated anti-MPO antibodies without clinical vasculitis (Wang et al., 2013).

Other hypotheses include PTU and/or its metabolites accumulate in neutrophils and bind to MPO, altering its configuration and promoting autoantibody formation, PTU oxidization in the presence of activated neutrophils creates reactive drug metabolites that stimulate ANCA production, and PTU decreases the degradation of neutrophil extracellular traps, resulting in autoimmunity (Nakazawa et al., 2012).

C) Hydralazine:

A 2009 review of the literature found 68 hydralazine vasculitis reports (mean duration of drug exposure 4.7 years; mean dose 142 mg/d). Similar to the findings by Choi et al. kidney disease was common on presentation (81%), and patients had additional serologic evidence of an autoimmune process (96% ANA positive, 26% anti-dsDNA antibody positive, and 44% hypocomplementemia). Combined pulmonary-renal syndrome with hydralazine-associated AAV is rare, with only 15 suspected cases in the literature. Given the overlap in the clinical presentation of hydralazine-associated SLE and AAV, both diagnoses should be considered (Agarwal et al., 2014).
Hypotheses for the mechanism of hydralazine-associated AAV include neutrophil apoptosis in response to hydralazine MPO binding, resulting in the production of multiple autoantibodies, increased expression of neutrophil autoantigens through hydralazine-induced reversal of epigenic silencing of MPO and PR3, and a break in tolerance in slow versus fast acetylators of hydralazine (Pendergraft and Niles, 2014).

D) Other Drugs:

Initial reports linked minocycline to AAV, but subsequent data on this association are conflicting. A cross-sectional study in patients of dermatology found ANCA positivity in 12 of 174 (7%) of patients with past/ current minocycline use compared with zero of 71 patients without exposure (Ortega et al., 2007).

Polyarteritis nodosa (PAN) with p-ANCA positivity, sometimes with renal involvement, has also been reported in patients exposed to minocycline. Fifteen patients with non PAN, minocycline AAV have been reported to date, but none had renal involvement (Lenert et al., 2013).

Allopurinol-associated vasculitis has been noted in case reports, but reports of serology-positive AAV are rare (Holder et al., 2002).

The association between the use of TNF-α inhibitors and AAV is not clear. A French survey–based registry of TNFα inhibitor AAV found it in 39 of 1200 patients, five of whom were ANCA positive. Another prospective series of patients with ankylosing spondylitis did not show a significant increase in ANCA seroconversion in treated patients. Six
patients with TNF-α inhibitor AAV have been reported to date (Tosovsky et al., 2012).

Case reports exist (some with renal involvement) for IFN AAV during treatment for hepatitis C. This is a challenging diagnosis, because autoantibodies (including ANCAs) may be seen with hepatitis C infection (commonly anti-PR3); also, the presentation of AAV may overlap clinically with cryoglobulinemic vasculitis (Palazzi et al., 2012).

Both isoniazid and rifampin have been implicated as causes of vasculitis in case reports, but the association between these drugs and AAV is confounded by studies that have shown a high prevalence of positive ANCA serologies in patients with tuberculosis (Tan et al., 2014).

**DIL:**

❖ **Definition**

Although there are currently no formal classification criteria for the diagnosis of DIL, it is widely accepted that DIL is defined as the development of lupus-like symptoms (commonly fever, musculoskeletal involvement and serositis) that is temporally related to continuous drug exposure (>1 month) which resolves with cessation of the offending drug. It is usually accompanied by serologic findings of a positive ANA as well as anti-histone antibodies. Unlike idiopathic systemic lupus erythematosus (SLE), antibodies to dsDNA are rare (Sarzi-Puttini et al., 2005).

❖ **Epidemiology**

The age of onset of DIL is generally older; with an equal female to male distribution and has an estimated incidence of 15 000–20 000 cases
per year. Whites may be affected up to six times more frequently than blacks and may have more severe manifestations. Certain risk factors have been identified such as the slow acetylator status, HLA-DR4, HLA-DR0301, complement C4 null allele and the female gender (Atzeni et al., 2003).

**Clinical and serologic features**

The clinical spectrum of DIL ranges from limited cutaneous involvement to a systemic form that is generally mild. The time between drug exposure to onset of symptoms varies from one month to as long as over a decade after initiation of the drug treatment. The onset is generally insidious (Yung and Richardson, 1994).

A. **DIL**

Patients commonly present with fever, arthalgia (90%) or arthritis, myalgia (50%) and serositis. These symptoms are usually mild although life-threatening cases have been reported. The classic malar or discoid rash, oral ulcers and major organ involvement (renal and neurologic) seen in idiopathic SLE are notably rare in DIL (Table 6) (Graziadei et al., 2003).

Laboratory findings may include mild cytopenia and an elevated erythrocyte sedimentation rate. Although most patients typically have a ANA, the incidence is variable. The ANA pattern is consistently homogenous as the autoantibodies target nuclear histone proteins. Anti-histone antibodies are positive in up to 95% of DIL while anti-dsDNA antibodies are rare; in contrast to idiopathic SLE (Table 6) (Callen, 2001).
Longitudinal studies have shown that the ANA and anti-histone titres gradually decline with the resolution of DIL. Another distinguishing feature of ANA in DIL is that these antibodies are not complement fixing, unlike those in SLE. Finally, it has been demonstrated that various subnucleosome particles within the histone-DNA complex in the cell nucleus, have varying antigenicity across different drugs in DIL. For example the (H2A-H2B)-DNA complex is the predominant antigenic particle in procainamide-induced SLE (Rubin et al., 2004).

Anti-histone antibodies albeit more prevalent, are however not pathognomonic of DIL as they are found in SLE and have been reported in other rheumatic diseases such as scleroderma, rheumatoid arthritis and undifferentiated connective tissue disease. This apparent paradox has led to postulate that the metabolites of offending drugs have the capacity to non-specifically disrupt central immune tolerance to chromatin which alludes to the pathomechanism of idiopathic SLE as well (Rubin, 2005).

B. Drug-induced subacute cutaneous LE(SCLE)

SCLE is similar to idiopathic SCLE in terms of clinical and serologic characteristics and is less prevalent than the systemic form of DIL. In a retrospective review of 70 patients with biopsy-proven SCLE, 21% had drug induced SCLE and the most commonly implicated drugs were namely antihypertensive agents (thiazide diuretics, angiotensin-converting enzyme inhibitors and calcium-channel blockers). More recently, terbinafine, an oral anti-fungal agent; bupropion, an antidepressant and acebutolol, a beta-blocker have been described as probable offending agents (Fenniche et al., 2005).
C) Drugs exacerbating underlying SLE

In DIL, years of exposure to steady-state levels of the offending drug are required for the development of this syndrome. Conversely, exposure to low levels of certain drugs for relatively short periods leads to exacerbation of underlying SLE. A wide variety of drugs have been implicated in causing lupus flares and these include antibiotics particularly sulfonamides, anticonvulsants and NSAIDs and estrogens (Capponi et al., 2005).

The results of a recent multicentre SELENA trial (Safety of Estrogens in Lupus Erythematosus, National Assessment) have helped to clarify the controversy over exogenous hormones and lupus flare risk. It demonstrated that the use of oral contraceptives in premenopausal women with stable or inactive SLE was not associated with an increased flare risk. In the postmenopausal arm, short course hormone replacement therapy was associated with a significantly increased risk of mild to moderate lupus flares ($P < 0.01$). In both arms, women with a history of thrombosis or high titre anti phospholipid antibodies were excluded (Petri et al., 2005).

Table 5: Contrasting characteristics of DIL and idiopathic SLE (Graziadei et al., 2003).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DIL</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Older</td>
<td>Child-bearing years</td>
</tr>
<tr>
<td>Female : male</td>
<td>1:1</td>
<td>9:1</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Remits with drug cessation</td>
<td>Chronic, relapsing</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>Generally mild</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Major organ involvement</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Cutaneous involvement</td>
<td>Purpura, erythema nodosum SCLE</td>
<td>Malar, discoid rash, photosensitivity, oral ulcers</td>
</tr>
<tr>
<td>Serologic features</td>
<td>ANA (homogenous)</td>
<td>ANA (homogenous, speckled)</td>
</tr>
<tr>
<td></td>
<td>Anti-histone (up to 95%)</td>
<td>Anti-histone (up to 50%)</td>
</tr>
<tr>
<td></td>
<td>Anti-dsDNA (&lt;5%)</td>
<td>Anti-dsDNA (50–70%)</td>
</tr>
</tbody>
</table>
Pathogenesis of DIL

The pathomechanisms in drug-induced lupus is unlike classical drug hypersensitivity reactions for several reasons: first, it lacks drug-specific T-cells or antibodies and the target autoantigens are not directly affected by the offending drug. Second, the time course for the development of DIL tends to be much slower than that of classic drug hypersensitivity. Furthermore, reintroduction with a lupus-inducing drug is not associated with memory of prior exposure if systemic autoimmunity had normalized. Finally, the duration of exposure and drug dose affects the likelihood of development of DIL. Four main mechanisms have been hypothesized in the literature to date (Uetrecht, 2005).

A) Hapten hypothesis

Either the drug or its metabolite binds to protein (hapten), thus making it ‘foreign’ and incites an immune response against the hapten or possibly self-antigens by virtue of molecular mimicry or antigen processing, resulting in presentation of cryptic antigens (Uetrecht et al., 1998).

B) Direct cytotoxicity hypothesis

Certain reactive drug metabolites may directly cause cell death via a non-immune mediated process. This has been demonstrated a wide variety of lupus inducing drugs in vitro. However, this process cannot entirely explain the immune perturbations in DIL. Hence, it has been postulated with a paucity of evidence that drug metabolites also alter degradation and clearance of apoptotic cells which eventually leads to the loss of tolerance to self-antigens (Williams et al., 2000).
C) Lymphocyte activation hypothesis

Murine splenocytes exposed to procainamide or hydralazine in vitro demonstrated an increased proliferative response to autologous antigen-presenting cells without the need for cognate antigen and promoted B cell differentiation in antibody-secreting cells. Adoptive transfer of such cells induced a lupus-like syndrome in mice (Yung et al., 1995).

D) Disruption of central immune tolerance

Murine models have shown that intra-thymic injections of lupus-inducing drugs resulted in a delayed but sustained production of anti-chromatin antibodies. It was subsequently demonstrated that these drugs interfered with the establishment of tolerance to endogenous self-antigens that are normally presented by the MHC to thymocytes. Hence mature T-cells are capable of undergoing spontaneous activation when encountering similar self-antigens in the periphery (Kretz-Rommel and Rubin, 2000).
Drugs Associated with DIL:

Below in table (6) some of drug categories entangled in DIL

Table 6: Drugs and risk for developing drug-induced lupus (Vasoo, 2006).

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Risk for Drug-Induced Lupus</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Procainamide</td>
<td>Quinidine</td>
<td></td>
<td></td>
<td>Disopyramide, propafenone, amiodarone</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Hydralazine</td>
<td>Methyl dopa, captopril, acebutolol</td>
<td>Enalapril, lisinopril, clonidine, atenolol, labetalol, pindolol, minoxidil, prazosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine,</td>
<td>Phenelzine, chlorprothixene, lithium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Isoniazid, minocycline</td>
<td>Nalidixic acid, sulfamethoxazole, quinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
<td>Clobazam, phenytoin, trimethadione, primidone, ethosuximide, valproic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithyroid</td>
<td>Propylthiouracil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td>Chlorthalidone, hydrochlorothiazide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td>TNF-α inhibitors</td>
<td>IFN-α</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Statins, levodopa, aminoglutethimide, timolol drops, ticlodipine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A) Procainamide.

DIL is most closely associated with procainamide; 80%–90% of patients develop a positive ANA over 2 years of therapy, and approximately 20%–30% develop DIL. Middle-aged men are most commonly affected, likely because of increased prescription in this population. Presentation with pulmonary symptoms and serositis is
common, whereas arthritis and major organ involvement (including the kidney) are rare (Xiao and Chang, 2014).

Although the exact mechanism of procainamide DIL is unclear, in a small study of 20 patients receiving chronic procainamide therapy, patients who were slow acetylators developed antinuclear antibodies sooner (2.9 months) than fast acetylators (7.3 months). Procainamide was also found to be a potent T cell activator through a hypomethylation pathway in mice, leading to autoreactivity and autoimmunity (Araú et al., 2014).

B) Hydralazine.

Renal involvement is uncommon in hydralazine DIL. In one case series, hydralazine DIL occurred in 14 of 281 (5%) patients. Six patients had evidence of renal involvement. These six patients were all women, were taking 50–300 mg/d hydralazine for 0.5–7 years, and commonly had positive ANA (100%), anti-dsDNA antibody (66%), and hypocomplementemia (50%). All patients were slow acetylators, and four had HLA-DR4 genotype. The patients improved after stopping hydralazine and treatment with immunosuppressive therapy. Like with procainamide, slow acetylators have an increased risk of hydralazine DIL versus fast acetylators, and studies have found an increased frequency of HLA-DR4 antigens in patients with hydralazine DIL (Vasoo, 2006).

C) Biologic Agents, Including TNFa Inhibitors.

Piga et al. found 26 patients with biologic-associated (including TNF-α inhibitors) autoimmune renal disease through a cohort study analysis and literature review. On the basis of clinical manifestations and renal histology, patients were classified into GN associated with systemic
vasculitis (GNSV), GN in lupus-like syndrome, and isolated autoimmune renal disorders (IARDs). TNF-α inhibitors included etanercept (15 patients; 51.7%), adalimumab (nine patients; 31.0%), and infliximab (three patients; 10.3%) (*Piga et al., 2014*).

C) Other drugs associated with DIL

Including *tocilizumab* and *abatacept* (one patient each; 3.4% each); 13 of 29 (44.8%) patients were classified with IARD, 12 (41.3%) patients were classified with GNSV, and four (13.9%) patients were classified with GN in lupus like syndrome. A worse outcome was associated with GNSV and continued use of biologics; end stage renal failure was reported in three patients with GNSV and one patient with IARD, and one death was reported in GNSV (*Piga et al., 2014*).

In a review of 25 published case reports of TNF-α inhibitor DIL, skin involvement occurred in 67% of patients, renal manifestations were noted in 7% of patients, anti-dsDNA antibodies were common (72%), and low complements occurred in 17%. Similarly, in a French Registry, cutaneous manifestations alone were seen in 10 patients, and systemic symptoms (without renal involvement) were found in 12 of 866 patients (*Ramos-Casals et al., 2007*).

Symptoms began approximately 6 months after drug initiation and took 1–4 months to resolve after discontinuation (*Piga et al., 2014*).

The proposed pathogenesis of anti–TNF-α DIL differs from that of other agents. Low TNF-α levels lead to severe lupus-like autoimmunity, and recombinant TNF-α delays the development of lupus in the mouse model. Several theories have been proposed to explain TNF-α inhibitor DIL. In the cytokine shift paradigm, TNF-α blockade suppresses
Chapter III  Drug-induced glomerular Disease: Immune-mediated injury

production of T helper 1 (Th1) cytokines, driving the immune response toward Th2 cytokine production, IL-10, and IFN-α. The resulting cytokine imbalance results in autoantibody production and lupus manifestations. Furthermore, anti–TNF-α drugs may induce apoptosis in inflammatory cells, releasing autoantigens that stimulate autoantibody formation (Gonnet-Gracia et al., 2008).

It is important to note that improvement in lupus symptoms after stopping anti–TNF-α drugs is the only way to determine whether the latter agent was implicated in causing DIL (Piga et al., 2014).

Table 7: Comparison of clinical and laboratory features of three drugs associated with drug-induced lupus (Xiao and Chang, 2014).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Features</th>
<th>Laboratory Features</th>
<th>Positive Antibody Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>Rash, fever, myalgias, pleuritis, polyarthritis nephritis &lt;10%</td>
<td>Anemia, leukopenia</td>
<td>ANA, anti-dsDNA, ANCA, antihistone</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Polyarthritis, polyarthralgias serositis nephritis &lt;10%</td>
<td>Anemia</td>
<td>Anti-dsDNA, antihistone, antcardiolipin</td>
</tr>
<tr>
<td>TNF-α inhibitors</td>
<td>Systemic symptoms predominant (nephritis in 7%); skin manifestations dominate</td>
<td>Thrombocytopenia, hypocomplementemia</td>
<td>ANA, anti-dsDNA, ant nucleosome, antcardiolipin</td>
</tr>
</tbody>
</table>
Treatment and Prognosis

There are few data and no randomized trials or guidelines for the treatment of DIL. The first step is to withdraw the offending agent. Symptoms typically resolve in days to weeks, although serologic abnormalities may take months to resolve. If disease persists, both antimalarials and corticosteroids have been used for symptoms, such as serositis, and NSAIDs have been used for arthritis. The involvement of major organs (especially kidneys, brain, lungs, and heart) requires escalation of immunosuppressive therapy, such as in SLE, with high-dose corticosteroids, antimetabolites, or alkylating agents (Ramos-Casals et al., 2007).

The prognosis for recovery is good, except when severe major organ involvement occurs. Significant organ damage and death have been reported under these circumstances, especially with TNF-α inhibitors (Piga et al., 2014).

Drug-induced membranous nephropathy (DIMN)

MN is the most common etiology of primary nephrotic syndrome in white adults. The majority of patients with MN have primary disease, and most patients with primary MN have autoantibodies directed against the phospholipase A2 receptor (PLA2R). In contrast, 25%–30% of patients have secondary forms of disease. In a review of nine published series on MN, 6.6% of patients represented drug-induced disease. A more recent cohort identified a drug-induced etiology in 14% of patients. Testing for anti-PLA2R antibodies should be performed on renal biopsies or serum in patients with MN. The finding of anti-PLA2R antibodies in glomeruli or serum, strongly supports the diagnosis of primary MN and excludes a secondary drug–induced form of disease (Beck et al., 2009).
The pathogenesis DIMN

It likely involves an immune response to a therapeutic agent or its byproduct. The most plausible mechanism is that cationic drug–derived antigens traverse the GBM, are planted at the subepithelial aspect of the GBM, and become bound in situ to circulating antibodies directed against these antigens. This mechanism underlies the early-childhood MN that occurs in response to cationic BSA present in cow’s milk (Debiec et al., 2011).

Pathology:

MN is defined by subepithelial immune complex deposits and associated GBM alterations that include intervening spike formation, overly neomembrane formation, and remodeling (Figure 6). Pathologic findings do not distinguish between primary MN and DIMN (Beck et al., 2009).
Figure 6: A glomerulus from a patient who developed nephrotic syndrome while receiving a nonsteroidal anti-inflammatory drug for arthritis. The glomerulus exhibits global thickening of the glomerular basement with spike formation, which is characteristic of stage 2 membranous changes. Jones methenamine silver, 3400 (Beck et al., 2009).

Treatment of DIMN:

It begins with withdrawal of the culprit drug. In the case of some therapeutic agents, such as gold salts, penicillamine, and bucillamine, proteinuria and MN are so frequent that urine monitoring is required. With severe symptoms of nephrotic syndrome and/or lack of improvement after withdrawal, immunosuppressive therapy may be warranted (Beck et al., 2009).
Drugs Associated with MN

A) Gold Therapy:

Gold salts, including oral and parenteral preparations, have been used in the treatment of RA for more than three quarters of a century, but recently, they have been largely replaced by safer, more efficacious agents. The most common side effect of gold is proteinuria, which develops in 3%–7% of patients. Renal biopsy most commonly reveals stage 1 or 2 MN, indicating early detection because of screening. After withdrawal, proteinuria resolves in most patients. Experimental studies have shown that gold inclusions mainly localize to proximal tubules, and the same is true in a rodent model of gold induced MN, suggesting that gold targets tubular epithelium and leads to release of tubular antigens that cross-react with podocyte antigens (Jonathan et al., 2015).

B) Penicillamine and Bucillamine:

Penicillamine and bucillamine are used to treat RA, proteinuria is the most frequent indication for discontinuing therapy, and the most common biopsy finding is MN stage 1. Penicillamine has been used to treat RA for nearly 50 years, and the incidence of proteinuria may exceed 10%. Outcomes after penicillamine withdrawal are excellent, with complete resolution of proteinuria in the absence of immunosuppression in 32 of 33 patients in one series. Bucillamine is a more recently developed antirheumatic drug that is mainly used in Asia and differs from penicillamine by an additional sulfhydryl group. Similar to penicillamine, proteinuria resolves in nearly all patients after withdrawal. The mechanism by which penicillamine and bucillamine produce MN is unknown but may involve modification of the immune response and/or hapten formation (Obayashi et al., 2003).
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C) Mercury

Mercury exposure is associated with severe toxicity involving multiple organ systems, most notably the central nervous system. Sources of mercury include contaminated foods (in particular, fish), dental amalgams, cosmetics, occupational exposures, and skin-lightening creams. Chronic mercury exposure is infrequently associated with NS and in most cases, MN. After discontinuation, remission of proteinuria occurs in most patients (Li et al., 2010).

A recent report described two patients who developed DIMN after the use of skin creams that contained mercury. The absence of anti-PLA2R antibodies in these two patients as well as the previously established rat model of mercury-induced MN provide support for the association between mercury and MN (Chakera et al., 2011).

D) Captopril:

Captopril is an angiotensin-converting enzyme inhibitor (ACE-I) that is commonly used to treat hypertension and reduce proteinuria.

Captopril seems to be the only ACE-I associated with the development of NS and in most cases, biopsy findings of MN. This complication of therapy, which is seen in up to 1% of patients, has been attributed to a sulphhydryl group, which is unique to captopril among the ACE-I s but a feature that it shares in common with penicillamine and bucillamine. After discontinuation, significant reduction in proteinuria commonly occurs (Jonathan et al., 2015).
E) NSAIDs

NSAIDs are widely used for their analgesic, antipyretic, and anti-inflammatory properties. NSAIDs inhibit cyclooxygenase-1 (COX-1) and COX-2, thereby blocking prostaglandin, prostacyclin, and thromboxane production. MN has been reported after the use of multiple classes of NSAIDs with varying chemical structures, including propionic acid derivatives (ketoprofen, fenoprofen, and ibuprofen), acetic acid derivatives (diclofenac, sulindac, and tolmetin), enolic acid derivatives (piroxicam), and selective COX-2 inhibitors (etodolac and celecoxib) (Markowitz et al., 2003).

The development of MN with these diverse agents suggests a mechanism of DIMN that likely involves the common pharmacologic effects of NSAIDs on mediators of inflammation. Given the widespread use of NSAIDs, the incidence of NSAID-associated MN is difficult to determine. A stringent criterion for this diagnosis is the requirement for rapid remission after withdrawal. Radford et al., examined NSAID-associated MN over a 20-year period at the Mayo Clinic. Considering only patients with stage 1 or early stage 2 MN, 29 of 125 patients were taking NSAIDs, and 13 had a rapid remission after drug withdrawal, suggesting that NSAID-associated MN represented 10% of patients with early MN (Radford et al., 1996).
Summary

Drugs and toxins are well established causes of renal tubulointerstitial injury, however drug-induced glomerular diseases are also an important concern for clinicians.

The glomerular insult associated with drug exposure can be broadly classified into two specific forms: (1) direct cellular toxicity and (2) immune mediated injury.

Direct glomerular cell injury, involving the mesangial, endothelial and visceral epithelial cells.

- Visceral epithelial cell, drug induced podocytopathy can occur in a number of situations.

IFN therapy is associated with podocyte injury that can manifest as nephrotic syndrome and histologic lesions, including MCD or FSGS, of both the collapsing and noncollapsing variety.

Pamidronate in high doses cause direct podocyte injury with impaired cell energetics, disrupted cytoskeleton, or altered cell signaling.

Chronic lithium exposure can be associated with MCD and less commonly FSGS.

NSAIDs may be a cause of MCD which may be because of shunting of AA metabolites into pathways that alter immune function and promote podocyte injury.

Both sirolimus, and androgenic anabolic steroids frequently abused by bodybuilder can cause FSGS lesion seen on biopsy.
**summary**

- **Endothelial cell**: TMA is a severe form of endothelial injury that occurs systemically and within the renal parenchyma. A drug induced etiology should always be considered including chemotherapeutic agents, IFN, antiplatelet agents, calcineurin inhibitors and quinine.

- **Mesangial cell injury**: Nodular glomerulosclerosis has emerged as a specific lesion associated with cigarettes smoking.

**Immune mediated injury**: Exposure to certain drugs can elicit an immune response that result in generation of autoantibodies and clinical autoimmune disease, including immune complex or pauci immune GN.

- **ANCA associated vasculitis**: Drugs commonly implicated in AAV involve cocaine, levamisole, hydralazine, antithyroid medications, minocycline, allopurinol, penicillamine, and sulfasalazine.

- **Drug induced lupus**: The drugs commonly associated with DIL are hydralazine, procainamide, and anti-TNF therapy.

- **Membranous nephropathy**, which can be induced by gold salts, captopril (the only ACE-I), and NSAIDs.

**Finally** we conclude that, a variety of drugs have the capacity to induce glomerular injury. These drug induced glomerular disease should be part of the differential diagnosis in patients presenting with proteinuria, hematuria, and/or renal insufficiency. Recognition of a drug induced etiology and withdrawal the offending drug providing the best hope of renal recovery.
Reference


Reference

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الفريق العربي

هناك عدد كبير من الأدوية قد يسبب أمراض الكلى الحادة والمزمنة. إثبات علاقة الدواء بحدوث المرض يواجه العديد من التحديات ولكن هناك بعض من الطرق لتأكيد هذه العلاقة، ومنها استبعاد المسببات الأخرى والمتابعة، تكرار حدوث المرض مع تكرار استخدام الدواء، وقياس نسبة الدواء في دم المريض.

الكيبية الكلوية هو عضو عالي التخصص يتكون من مجموعة من الخلايا أمثال (الخلايا الحبيبية والخلايا المبطنة للشعيرات الدموية وخلايا مسراق) وغشاء قاعدي ومسراق الكيبية. إصابة أي جزء من هذا النموذج يؤدي إلى حدوث أعراض وآمراض مختلفة.

الأدوية المسببة لأمراض الكيبيات الكلوية عن طريق إصابة مباشرة تقسم على أساس الخلية المصابة في الكيبية الكلوية إلى ثلاث أنواع من الإصابات. وتضم إصابة الخلية البطانية، إصابة خليفة مسراق، ويحدث هذا عن طريق مجموعة من الأدوية الشائعة الاستخدام مثل الإنترفيرون، مضادات الأنتيبرويد، ومضادات الصفائح الدموية.

إصابة الخلية الجهازية وتشمل كل من مرض الحد الأدنى من التغيير وتشمل الأدوية المسببة له كل من الأنتريفيرون، الليثيوم ومضادات الأنتيبرويد. كما تشمل مرض تصلب الكيبيات البؤري القطاعي ومن الأدوية المسببة له كل من الأنتريفيرون، الليثيوم، والسيرويليمس. وعلى الرغم من أن هناك تشابه بين الأدوية المسببة لمرضين إلا أن تحول أحدهما للأخر غير مفروض.

إصابة الخلية البطانية وتشمل مرض إعتلال الأوعية الدقيقة الخثاري. ويطلق هذا المصطلح على مجموعة من الأمراض التي تحمل أوجه من التشابهات الباثولوجية والأكلينيكية. ويشمل هذا المرض تكسر كرات الدم الحمراء.
ونقص في الصفائح الدموية بالإضافة إلى اعتلال وظائف بعض من أعضاء الجسم. ومن الأدوية التي قد تسبب حدوث هذا الاعتلال ميتوميسين، إنترفيرون، ثينوبيردين، والكينين.

إصابة خلايا مسراق يؤدي إلى مرض الكبيبات القيدية مجهولة السبب، وبعد التدخين الشره من المسببات الرئيسية لهذا الاعتلال.

الأدوية المسببة لأمراض الكبيبات الكلوية عن طريق تنشيط الجهاز المناعي

التعرض لبعض الأدوية يستطيع تحفيز رد مناعي ينتج عنه تكوين أجسام مضادة وأمراض مناعية. وعند المعالج بهذه العلاقة والتفريق بينها وبين الأمراض الأولية هو من أساسيات نجاح العلاج.

التهاب الأوعية الدموية المصاحب للأجسام المضادة انكا. نشأت بعض من النظريات التي تربط حدوث التهابات بالأدوية وبدأت هذه النظريات إكتشاف الجسم المضاد انكا. ومن الأدوية المسببة لهذه الالتهابات، الكوكابين، ليفاميسول، هيدراايلين، الأدوية المثبطة للغدة الدرقية، مينوسيلين، الوبرينول، بينسلافين، و السلفاسلاتين.

الأدوية المسببة لمرض الذببة. ومن الأدوية المشهورة لحدث هذه الحالة هم دواء الهيدراايزين ودواء البوكناميد. ومقارنة بمرض الذببة النمراء الأصلي إيقاف إستخدام هذه الأدوية يؤدي إلى تحسن الأعراض، بالإضافة إلى أنه لا يوجد ميل جنس عن الآخر كما في حال مرض الذببة الأصلي الذي يميل إلى الحدوث أكثر في السيدات.

الأدوية المسببة لاعتلال الكلية الغشائي، وتشمل أملاح الذهاب التي تستخدم في علاج مرض الروماتيزم، ودواء الكابتوبيريل الذي يستخدم في علاج ارتفاع ضغط الدم.
الأدوية المسببة لأمراض الكبيبات الكلوية

رسالة

للحصول على درجة الماجستير في الباطنة العامة

مقررة

الطبيب/ أحمد عبدالرحمن السيد حفناوى

بكالوريوس الطب والجراحة

تم إثراء

الأستاذ الدكتور/المتولى لطفي الشهاوى

أستاذ الباطنة العامة و أمراض الكلي
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أستاذ الباطنة العامة و أمراض الكلي
كلية الطب - جامعة بنها

الدكتور / محمد الطنطاوي إبراهيم

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2017