Secondary Glomerular Disease and Renal Vasculitis

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Introduction

In this chapter each condition including ANCA associated vasculitis, lupus nephritis, cryoglobulinemia, protein deposition diseases, thrombotic microangiopathies is introduced separately with a typical case which is followed by epidemiology, clinical presentation investigations and management. The typical presentations and histological features of primary glomerulonephritis are presented in Chap. 12.

Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis

Clinical Scenario

A 67-year-old man presents with a 2 month history of fatigue, weight loss and myalgia. On examination he had a temperature of 37.7 °C, was pale and there was evidence of non-blanching, petechial rash on the dorsum of his feet. Urinalysis was positive for blood (+++) and protein (++). He had evidence of acute kidney injury with a serum Creatinine (Cr) of 387 μmol/L, having been normal 12 months previously. He was anaemic (Haemoglobin 97 g/L), with a raised white cell count (13.4×10^9/L) and CRP of 87 mg/L. He was referred to nephrology for assessment of his AKI.

Introduction

ANCA associated vasculitis (AAV) refers to a group of systemic autoimmune diseases with a wide range of clinical presentations. Vasculitis with kidney involvement typically causes a pauci-immune necrotising glomerulonephritis with crescent formation. There are several subtypes of AAV including; microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) [1]. Although each subtype has distinct features there is significant overlap in clinical presentations, investigation and treatment.

Epidemiology and Causes

The incidence of AAV is approximately 15–20 per million population per year, increasing with age, peaking in the seventh–eighth decade of life with a male predominance. AAV is less common in African populations and there is also geographical variation in the subtypes with GPA

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more common in Northern Europe and MPA more common in Southern Europe and Asia, probably reflecting both environmental and genetic factors.

Defects in immune regulation lead to the development of autoantibodies again constituents of neutrophil primary granules due to a combination of environmental triggers in people with a genetic predisposition.

Clinical Presentation

Previously the AAV subtypes were classified according to clinical features, with GPA more commonly involving the lungs and upper respiratory tract. However, there is significant overlap in clinical presentation and renal limited disease can occur in the absence of other features of systemic disease. Classification of the disease on the basis of ANCA type may be better than the traditional clinical classification. Table 13.1 summarises the main clinical features of the two main subtypes of AAV.

EGPA is associated with asthma and eosinophilia. ANCA positivity is less common as is renal involvement (20%).

Relapse is common affecting 30–50% of patients in the 5 years after diagnosis. Risk factors for relapse include younger age, PR3-ANCA (and persistent positivity), GPA phenotype, lower cumulative cyclophosphamide dose and discontinuation of therapy. Recurrence can occur after transplantation in approximately 15–20% of cases.

Investigations

Patients will often have evidence of systemic inflammation with a raised WCC and CRP. ANCA is detected in the majority of cases. Immunofluorescence on neutrophils detects two patterns, cytoplasmic (cANCA) and perinuclear (pANCA). The antigens detected are two constituents of neutrophil primary granules, Proteinase 3 and Myeloperoxidase respectively. Further assessment is usually performed by antigen specific ELISA, which has now replaced immunofluorescence in many laboratories. ANCA can also be found in other inflammatory conditions and is therefore not specific for AAV. Also some patients with vasculitis are ANCA negative, but their clinical presentation and response to treatment are similar to ANCA positive cases. Table 13.2 summarises the prevalence of ANCA in different forms of vasculitis.

Kidney biopsy shows necrotising glomerulonephritis with crescent formation. Immune complex deposition is not seen on immunofluorescence microscopy. Tubulointerstitial inflammation may also be present.

Table 13.1 Clinical features of AAV

	MPA (MPO-ANCA)	GPA (PR3-ANCA)
Age	60–80 years	50–70 years
Pathology	Necrotising vasculitis	Necrotising vasculitis with granulomas
Systemic features (fatigue, myalgia, fever)	Common	Common
Renal involvement	Can present with AKI or CKD	Common with rapidly progressive glomerulonephritis
Upper respiratory tract involvement	Uncommon	Common with destructive granulomatous lesions (nasal collapse), sinusitis, otitis media, nose bleeds
Lung	Pulmonary haemorrhage. Pulmonary fibrosis can occur.	Cavitating, destructive lesions
Skin	Common, leukocytoclastic vasculitis	Common, leukocytoclastic vasculitis
Response to treatment	Worse outcomes, particularly if evidence of chronicity	More likely to relapse responds better to therapy with Rituximab
Risk of relapse	Lower	Higher

Differential Diagnosis

It is important to exclude infection as patients have evidence of systemic inflammation and require immunosuppressive treatment. Also, ANCA can be positive in some chronic infections, for example endocarditis. Testing for ANCA and kidney biopsy will differentiate from other forms of rapidly progressive glomerulonephritis.

Table 13.2 ANCA in vasculitis

	MPO-ANCA (pANCA)	PR3-ANCA (cANCA)	ANCA negative
MPA	60%	30%	10%
GPA	20%	75%	5%
EGPA	45%	5%	50%
Kidney-limited vasculitis	80%	10%	10%

Management

With typical clinical presentation of small vessel vasculitis, rapidly progressive disease and positive MPO or PR3 ANCA serology waiting for kidney biopsy or biopsy results should not delay treatment.

Management of AAV should be considered in two phases; induction and maintenance. Induction treatment involves the first 3–6 months of therapy and aims to reduce inflammation quickly. It is usually with a combination of corticosteroids with either cyclophosphamide or rituximab. If disease is resistant to one induction treatment switching to the alternative approach is recommended. It is important to tailor treatment regimens to patients as a significant proportion of the morbidity and mortality from AAV is treatment related. Relapse requires a further course of induction treatment. Table 13.3 summarises

Table 13.3 Induction treatment in ANCA associated vasculitis

	Rationale	Dose
Induction		
Corticosteroids	Anti-inflammatory	In severe disease (rapidly progressive GN or lung involvement) usually pulsed intravenous treatment (3 doses of methylprednisolone), followed by oral taper starting a 1 mg/kg prednisolone and reducing to maintenance dose by 3–6 months. Emerging evidence that lower doses of corticosteroid may be equally effective and safer [2]. See Table 13.4
Cyclophosphamide	Immunosuppressive action reducing lymphocyte proliferation	Used in combination with steroids. Can be given orally (2 mg/kg) or intravenously (15 mg/kg every 2–3 weeks). Intravenous treatment uses a lower cumulative dose and is associated with less marrow suppression but a higher relapse rate. Preferred with high or rising creatinine (>354 μmol/L)
Anti-CD20 monoclonal antibody (Rituximab)	B cell depletion	Used as an alternative to cyclophosphamide with evidence of non-inferiority for remission induction. Dosed either weekly 375 mg/m^2 or 1000 mg every 2 weeks. May be superior to cyclophosphamide in patients with PR3-ANCA. Removed by plasma exchange. It is may be preferred in children, adolescents, frail adults, premenopausal women, men concerned about fertility
Mycophenolic acid	Anti-proliferative. Suppression of lymphocyte responses	Can be used as an alternative to cyclophosphamide for induction for patients with less severe disease - 2000–3000 mg/day. Higher relapse rate
C5a Receptor antagonist (Avacopan)	Anti-inflammatory action by blocking the anaphylotoxin C5a	Can be used to reduce or avoid the use of corticosteroids as part of an induction regime

Table 13.4 Glucocorticoid dose used in Pexivas study

	Standard			Reduced-dose		
	<50 kg	50–75 kg	>75 kg	<50 kg	50–75 kg	>75 kg
Week	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3–4	40	50	60	20	25	30
5–6	30	40	50	15	20	25
7–8	25	30	40	12.5	15	20
9–10	20	25	30	10	12.5	15
11–12	15	20	25	7.5	10	12.5
13–14	12.5	15	20	6	7.5	10
15–16	10	10	15	5	5	7.5
17–18	10	10	15	5	5	7.5
19–20	7.5	7.5	10	5	5	5
21–22	7.5	7.5	7.5	5	5	5
23–52	5	5	5	5	5	5
>52	Investigators' local practice			Investigators' local practice		

induction treatment options; Table 13.4 summarises glucocorticoid/steroid use in the PEXIVAS study.

Maintenance therapy is then continued for 2–4 years to reduce the risk of relapse (Table 13.5). The optimal period of maintenance treatment is not known, but shorter treatment periods are associated with a higher rate of relapse.

Plasma exchange may be considered for patients with >Cr 500 μmol/L, requiring dialysis or with rapidly increasing Cr, and in patients with diffuse alveolar hemorrhage with hypoxia (or overlap with anti GBM).

Complement activation is involved in disease development and a recent trial has shown that C5a Receptor blockade can be an alternative to corticosteroids to induce remission. Plasma exchange was widely used as part of induction regimes, particularly for more severe disease. However, a recent report suggests that it does not improve outcome for patients with significant renal or pulmonary disease [2].

Table 13.5 Maintenance treatment in ANCA associated vasculitis

Maintenance	
Corticosteroids	Low dose corticosteroids are often included in maintenance regimes (in combination with another agent) but increasing evidence suggests that this may not be necessary
Azathioprine	Non-inferior to continued cyclophosphamide for the maintenance of remission
Mycophenolic acid	Can be used to maintain remission but associated with a higher rate of relapse compared to azathioprine
Anti-CD20 monoclonal antibody (Rituximab)	Good evidence that Rituximab can be used to maintain remission. 500 mg or 1000 mg every 6 months for 2 years. Low rate of relapse <10%

There is evidence that the use of antibiotics (Trimethoprim alone or in combination with sulphamethoxazole) to reduce nasal carriage of *Staphylococcus aureus* reduces the risk of relapse.

Other Forms of Vasculitis and the Kidney

Dual positive ANCA and anti-GBM disease. Approximately 10% of patients with AAV have anti-GBM antibodies. They have severe initial presentations (similar to anti-GBM disease) and are prone to relapse (similar to AAV).

Medium and large vessel vasculitis, including giant cell arteritis, Takayasu's arteritis (large vessel) and Kawasaki's disease and Polyarteritis nodosum do not cause glomerulonephritis but can affect the kidney. Renal involvement incudes renal artery stenosis, aneurysm formation, infraction and haemorrhage.

Drug induced vasculitis is reported due to a number of drugs including hydralazine, minocycline and anti-TNF drugs. ANCA can be positive in these cases.

Lupus Nephritis

Clinical Scenario

A 26 year old woman presented with pain and swelling in the joints of her hands and knees for the previous 6 weeks. On examination the MCP and PIP joints of both hands were swollen and tender to palpation. Urinalysis was positive for blood and protein. Initial investigation showed a mild anaemia (Hb 102 g/L) low white cell count (3.1×10^9/L) and a high Cr 122 μmol/L.

Introduction

Lupus nephritis (LN) affects approximately 50% of patients with systemic lupus erythematosus (SLE). It varies in severity from mild disease to severe rapidly progressive disease causing ESKD. The presence of significant renal involvement is associated with a poor prognosis.

Epidemiology and Causes

Females are more commonly affected by SLE than males (10 to 1) but the risk of LN is the same in female and male patients with SLE. The incidence is estimated at 2–5 per 100,000 population per year. African, Hispanic and Asian populations have more severe disease.

Defects in immune regulation and loss of tolerance lead to the development autoantibodies against a range of nuclear antigens. Both genetic (including HLA type) and environmental factors are implicated in disease development. The autoantibodies form immune complexes either in the circulation or locally in the kidney leading to complement activation and other inflammatory responses.

Clinical Presentation

The European League against Rheumatism/American College have developed a set of criteria for the diagnosis of SLE [3]. In patients with a known diagnosis of SLE the development of proteinuria (>0.5 g/24 h or equivalent) or cellular casts on urine microscopy indicates the development of LN. However significant renal damage can be present in patients with lower levels of proteinuria. Nephrotic syndrome is common, occurring in over 50% of patients with class IV and V LN. LN may develop in the absence of symptoms of SLE in patients who therefore do not fulfil current diagnostic criteria.

LN usually follows a protracted course, with periods of disease activity and remission. Reported rates of ESKD vary between 10 and 50% depending on era and population studied. Higher risk of ESKD is predicted by the presence of impaired renal function at presentation, black race and the class of disease on biopsy, patients with class IV LN having the worst prognosis. Clinically relevant recurrence after transplant is rare (<5%).

Investigations

The diagnosis of SLE is based on clinical and immunological criteria. Several different autoantibodies are often detectable (Table 13.6).

Table 13.6 Blood tests for patients with suspected SLE and LN

Antibody	Association with SLE and LN
Antinuclear antibodies (ANA)	Currently or historically positive in >95% of cases and required for the diagnosis of SLE based on recent criteria. Positive in other inflammatory diseases
Anti-dsDNA	A nuclear antigen, specific for SLE, but only positive in 75% of cases. High titres correlate with disease activity
Anti-Smith-(Sm)	Smith antigen is an RNA binding protein and antibodies are specific for SLE, but only positive in 25% of cases
Antibodies against other extractable nuclear antigens (nRNP, Ro, La)	Can be positive in SLE but are not specific and seen in other autoimmune diseases
Complement C3 and C4	Reduced in LN and low levels are associated with active disease

Table 13.7 ISN/RPS classification of LN

	Histological features
Class I	Minimal mesangial changes. Normal light microscopy mesangial with immune deposits
Class II	Mesangial hypercellularity or matrix expansion with mesangial IC deposition
Class III	Focal segmental or global endocapillary or extracapillary glomerulonephritis involving <50% of glomeruli, typically with focal subendothelial immune deposits. Includes assessment of active (A) or chronic (C) lesions
Class IV	Diffuse segmental or global endocapillary or extracapillary glomerulonephritis involving >50% of glomeruli, typically with difffuse subendothelial immune deposits. Includes assessment of active (A) or chronic (C) lesions
Class V	Membranous lupus nephritis with global or segmental immune deposits
Class VI	Advanced sclerosing LN (>90% glomerular sclerosis)

Other results including anaemia, thrombocytopenia and low white cell count are also typical and may correlate with disease activity. Proteinuria indicates renal involvement and should be part of the assessment of all patients with SLE.

Kidney biopsy is important in the assessment of LN. There is significant diversity in glomerular findings, between patients and histology can change in an individual patient over time and in response to treatment. Biopsy findings are classified according to the International Society of Nephrology/Renal Pathology Society classification (Table 13.7) [4] and the class of disease predicts prognosis and is used to determine the treatment required.

The detection of immune deposits by immunofluorescence and electron microscopy is a common feature in LN. Deposits will usually contain IgG but also IgM, IgA, C3 and C1q. When all are seen, this pattern is highly suggestive of LN.

Differential Diagnosis

Clinically other connective tissue disease can mimic SLE. Diagnosis is made from the pattern of symptoms and testing for autoantibodies.

Management

The treatment of LN is dependent on the class of disease and is aimed at preventing progressive kidney injury. Standard treatment includes the use of ACE inhibitors or angiotensin receptor blockers and hydroxychloroquine. Subsequent treatment is then determined by the class of LN.

Class I and II

This is associated with a good prognosis and therapy is directed to extra-renal involvement. Class I and II LN can evolve into more aggressive disease, so long-term monitoring is required.

Class III

Milder forms of class III LN with infrequent proliferative lesions, no necrotising lesions or crescents can be treated with a short course of immunosuppression, often corticosteroids. More severe class III LN should be treated a Class IV.

Class IV

There is no universally accepted treatment for Class IV LN and treatment has to be varied depending on a patient's clinical condition and previous treatment exposure. Corticosteroids in combination with another agent is the most commonly used treatment as corticosteroids alone are insufficient to control disease. Current European recommendations are for initial intravenous methylprednisolone [0.25–0.5 g/day for 1–3 days] followed by oral steroids starting at 0.3–0.5 mg/kg (reduced dose) for 4 weeks [or 0.6–1 mg/kg/day] then tapered over 3 months [5].

Steroids are combined with cyclophosphamide, usually administered intravenously, or mycophenolate mofetil (MMF) / mycophenolate sodium which have similar efficacy, with MMF potentially being better in black patients. The dose of MMF should be 2–3 g/day (MPA 1.44–2.16 g/day) and cyclophosphamide dosing should usually follow the low dose Euro-Lupus regime [0.6 g every 2 weeks, 6 doses] which has equivalent long-term outcomes compared to higher dose regimes [0.5–1 g/m^2/month for 6 months] [6].

Calcineurin inhibition with either cyclosporine or tacrolimus [trough level 5.5 ng/L] has been used either as monotherapy or in combination (for example with MMF). Although there are some promising results, further data is required before this can be recommended as a first line treatment. Voclosporin 23.5 mg BD can be used with MPA for 52 weeks in patients with eGFR > 45 mL/min/1.73 m^2.

In patients with refractory disease switching to an alternative treatment regime should be considered. The addition of anti-CD20 (Rituximab or Obinutuzumab) or anti-BLyS (Belimumab 10 mg/kg every 2 week for 6 weeks and every 4 week with MPA or cyclo) monoclonal antibody treatment can also be considered.

Class V

MMF/MPA with glucocorticoid is the usual first choice treatment with calcineurin inhibition, either alone or in combination with MMF/MPA) is an alternative option. There is some evidence for Rituximab in patients who have not responded to first line treatment.

Rapid and complete remission, with proteinuria <0.5 g/day, is associated with better long-term outcomes. However, relapse occurs in approximately 50% of patients and requires further induction treatment. Relapse can be predicted by rising anti-dsDNA titres and falling complement (C3 and C4) concentrations.

Once remission is achieved patients should remain on maintenance treatment for a period of at least 5 years. MMF/MPA [1–2 g/day] or azathioprine [1.5–2 mg/kg/day] can be used with current the recommendation to continue MMF/MPA if remission was induced by these agents and to use either MMF/MPA or azathioprine if remission was induced by cyclophosphamide.

Antiphospholipid Syndrome

Antiphospholipid (APL) antibody syndrome (APS) is associated with IgG or IgM autoantibodies to plasma proteins containing phospholipids including anticardiolipin and anti-β_2-glycoprotein I antibodies and lupus anticoagulant activity. Diagnostic criteria includes: a positive antibody test on two occasions at least 12 weeks apart, episodes of venous or arterial thrombosis and fetal loss. APS occurs in the absence of another autoimmune disease in 50% of cases (primary). Approximately 30–50% of patients with SLE have detectable APL antibodies although a majority do not develop features of APS.

Renal involvement with APS (APL nephropathy) relates to vascular thrombosis ranging from the main renal artery or vein to glomerular capillaries and occurs in 25% of patients with APS. Vascular thrombosis is associated with an inflammatory, proliferative response. Other patterns of glomerular disease have also been reported. Thrombotic lesions on kidney biopsy can be seen in 10% of patients with SLE and is significantly higher in patients who have anti-APL antibodies.

Patients can present with hypertension, proteinuria and progressive renal dysfunction. Acute reduction in renal function can occur in the context of major vessel thrombosis and rapidly progressive GN has also been reported.

For patients with clinical features of APS warfarin treatment, aiming to maintain INR > 3, is the first line therapy. The role of immunosuppression, other than for the treatment of co-existing SLE, is uncertain.

Cryoglobulinaemia

Clinical Scenario

A 37 year old male intravenous drug user presents with a purpuric rash over his feet and lower part of his legs. He was noted to have non-visible haematuria and a Cr of 192 μmol/L. His liver functions tests were abnormal and he was found to be Hep C IgG positive. Complement C4 (0.04 mg/mL) and C3 (0.65 mg/mL) were both low.

Introduction

Cryoglobulins are circulating immunoglobulins that precipitate in the cold. They usually occur in the presence of underlying infection, autoim-

Table 13.8 Classification and cause of cryoglobulinaemia

	Immunoglobulin type	Cause
Type 1	Monoclonal (IgM > IgG)	Monoclonal gammopathy of renal significance, Waldenström macroglobulinaemia, multiple myeloma
Type 2	Monoclonal (IgMκ 90%) directed against polyclonal immunoglobulin	Hepatitis C, autoimmune disease and other infections
Type 3	Polyclonal IgG/IgM directed against polyclonal immunoglobulin	Hepatitis C, autoimmune disease and other infections

mune disease (particularly Sjögren's syndrome) or lymphoproliferative disease and are classified according to the type(s) or immunoglobulin involved (Table 13.8). Cryoglobulins can cause either hyperviscosity (particularly type 1) or a systemic vasculitic illness with skin, kidney and neurological involvement.

Epidemiology and Causes

Cryoglobulinaemia is an uncommon disease with kidney involvement in approximately 25–50% of cases. In the majority of cases an underlying cause can be identified. Type 1 is associated with a monoclonal immunoglobulin only whereas type 2 and 3 involve different types of immunoglobulin (mixed cryoglobulinaemia), with one component possessing Rheumatoid factor like activity.

Clinical Presentation

Systemic symptoms include malaise, Raynaud phenomenon, arthralgia, hepatosplenomegaly, peripheral neuropathy, skin involvement (common) with levido reticularis, purpuric rash and ulceration and gangrene (Type 1>2 and 3). Renal disease is present in approximately 50% of cases and typically leads to haematuria, proteinuria, hypertension and renal insufficiency. Nephrotic syndrome or rapidly progressive disease can occur.

Investigations

Detection of cryoglobulins can be difficult and requires careful handling of samples to maintain a constant temperature and prevent precipitation. A precipitate is seen on cooling of serum to 4 °C. Rheumatoid factor is positive in mixed cryoglobulinaemia. Liver function is often abnormal (>50% of cases) and complement C4 levels are often suppressed. A screen for an underlying cause will most frequently identify Hepatitis C infection in patients with mixed cryoglobulinaemia.

Kidney biopsy shows endocapillary proliferation with large subendothelial deposits which can fill the capillary lumen. Immunofluorescence is positive for IgG and IgM (with IgM often dominant) and also C3 and C1q.

Differential Diagnosis

There can be features of other systemic autoimmune disease and systemic vasculitis. The presence of cryoglobulins and the renal biopsy appearance are diagnostic of cryoglobulinaemia.

Management

Treatment is usually targeted at the underlying condition, either hepatitis, other infection, lymphoproliferative disease or autoimmune disease. A combination of corticosteroids with a cytotoxic agent or rituximab can be used in idiopathic disease. In severe cases with ulcerative skin involvement, peripheral gangrene or rapidly progressive GN plasma exchange, in addition to corticosteroids and cytotoxics should be considered.

Protein Deposition Diseases

Clinical Scenario

A 72 year old man presents with increasing ankle oedema. He has no other symptoms and other than peripheral oedema clinical examination is normal. He has significant proteinuria with an ACR of 128 mg/mmol and a serum albumin of 26 mg/L. His creatinine is normal. A kidney

biopsy shows deposition of hyaline material in the mesangium and capillary walls which shows apple green birefringence under polarised light on Congo red staining.

Introduction

Amyloid describes the deposition of protein fibrils in various organs. Approximately 25 proteins can form amyloid fibrils in association with Serum Amyloid P component and all demonstrate characteristic apple green birefringence under polarised light on Congo red staining.

Epidemiology and Causes

Renal amyloid is uncommon affecting approximately 10 per million population per year and is found in approximately 2% of kidney biopsies. AA and AL are the most common renal amyloidoses accounting for >80% of cases the remainder being due to hereditary amyloidoses. AL amyloid is caused by the deposition of a proportion of an immunoglobulin light chain ($\lambda > \kappa$, 12:1) produced by a clonal population of plasma cells. AA amyloid is due to the deposition Serum Amyloid A protein in chronic inflammatory conditions. The reason that amyloid fibrils form only in some patients is not known. Genetic variants in Fibrinogen A, transthyretin, apolipoproteins and leukocyte chemotactic factor 2 (LECT2) and other proteins can cause renal amyloid.

Clinical Presentation

AL amyloid usually involves the kidney and most patients will develop kidney disease at some point. The median age of presentation is 60 years with men affected twice as frequently as women. Patients present with oedema, fatigue, weight loss or painful neuropathy. Renal involvement is most common and is the only organ involved in 30% of cases. Most patients have proteinuria and 25% have nephrotic syndrome. A reduced GFR and hypertension are common. Cardiac (40%), peripheral nerve (25%), lymph node, liver and spleen (hepatosplenomegaly) involvement can occur. Multiple myeloma occurs in about 20% of patients with AL amyloid.

AA amyloid occurs in the context of chronic inflammation, due to chronic infection, inflammatory arthropathy or periodic fever syndromes. Renal involvement causes proteinuria and progressive decline in GFR. The presentation of hereditary amyloidosis is similar, and they can be difficult to distinguish form AL or AA amyloid.

Investigations

Renal amyloid is typically diagnosed in a biopsy from a patient being investigated for proteinuria although amyloid can be diagnosed on liver biopsy or less invasively on skin, fat pad or rectal biopsy. In patients with AL amyloid serum or urinary electrophoresis and immunofixation may show a monoclonal band and serum free light chains will show excess of either λ or κ light chain (monoclonal gammopathy of renal significance).

The injection of radiolabelled SAP (SAP scintigraphy) allows the extent of amyloid deposition to be determined. Genetic screening is required if hereditary amyloid is suspected.

Kidney biopsy demonstrates deposition of acellular hyaline material in the mesangium and capillary walls, which can be nodular, but is not stained by silver stain. Amyloid stains orange with Congo red and has a typical apple green birefringence under polarised light. Immunofluorescence for light λ or κ chains will stain AL amyloid deposits. In all types of amyloid electron microscopy typically shows 8–12 nm-wide fibrils.

Differential Diagnosis

Renal amyloidosis should be considered in older patients presenting with proteinuria. In some cases, there will be systemic symptoms to suggest amyloidosis but biopsy will often be required t distinguish renal amyloid from other proteinuric diseases.

Management

AL amyloid has a poor prognosis without treatment (median survival <2 years) with cardiac or renal involvement predicting a poor outcome. Prognosis has improved with the introduction of new treatments. If the patient is fit enough autologous stem cell transplantation (ASCT) should be considered otherwise chemotherapy (for example melphalan and corticosteroids) are effective. A response to treatment and reduction in light chain production (monitored by serum free light chain measurements) can lead to regression of deposits and good long-term outcomes. Bortezomib can also be used, often in combination with chemotherapy. The anti-CD38 monoclonal antibody, daratumumab, has shown promising results in the treatment of AL amyloid.

AA amyloid treatment is targeted at the underlying inflammatory disease. If inflammation can be suppressed with control of SAA protein concentration the prognosis is good (median survival >10 years) and amyloid deposits can regress.

In patients with ESKD due to amyloid transplantation can be considered if inflammation or the plasma cell clone is suppressed (usually after ASCT).

Other Forms of Protein Deposition Disease

Fibrillary glomerulonephritis, with 20 nm fibrils containing the chaperone protein DNAJB9 and IgG, can be idiopathic or occur in association with monoclonal gammopathies and malignancy. *Fibronectin nephropathy* is an autosomal dominant inherited disease that has a similar fibrillary structure, but the deposits contain fibronectin.

Immunotactoid glomerulonephritis is associated with larger (30–50 nm) hollow microtubules containing immunoglobulin which is commonly monoclonal. This disease has a poor prognosis, progresses rapidly to ESKD and is often associated with a lymphoproliferative disorder.

Monoclonal immunoglobulin deposition disease (MIDD) describes a group of diseases characterised by light chain, heavy chain or light and heavy chain deposition. *Light chain deposition disease* is most common, with granular, non-amyloid deposits of light chain (usually the constant region of κ). The median age of presentation is 50–60 years and an abnormal serum free light chain can usually be identified. On biopsy immunofluorescence for the abnormal immunoglobulin fragment is usually positive. Treatment is the same as for AL amyloid.

Thrombotic Microangiopathies (TMAs)

Clinical Scenario

A 12 year old girl presents with breathlessness and fatigue. She also reported passing 'coca-cola' coloured urine. Ten days previously she had 5 days of abdominal pain and diarrhoea which had resolved by the time she presented. On examination mucosal membranes were pale and blood pressure was raised at 148/108 mmHg. Urinalysis was positive for blood. Haematology screen showed a severe anaemia (Hb 54 g/L) and thrombocytopenia (Platelets 32 × 10^9/L). The blood film showed evidence of fragmentation. She had AKI with a Cr of 292 μmol/L.

Introduction

The thrombotic microangiopathies (TMAs) are a group of diseases characterised by microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and end organ damage due to small vessel thrombosis. Classically TMA was divided into two diseases depending upon the clinical presentation; Thrombotic Thrombocytopenic Purpura (TTP) in which neurological manifestations predominated and Haemolytic Uraemic Syndrome (HUS) in which kidney involvement was more common. However, there is significant overlap in clinical presentation and therefore it is more appropriate to consider TMAs according to their aetiology. Both TTP and HUS can be inherited or acquired.

Epidemiology and Causes

TTP is due to inherited (very rare) or acquired deficiency in a circulating enzyme, ADAMTS13 which is responsible for the breakdown of large multimers of von Willebrand factor. Reduced breakdown leads to activation of coagulation and thrombus formation. Acquired disease effect 5–10 per million population per year and is due to an inhibitory autoantibody.

HUS is most commonly due to infection with a shiga toxin producing enteropathogen, either *Escherichia coli* (STEC) or *Shigella,* which occurs after consumption of contaminated food. The toxin impairs endothelial function leading to thrombus formation. STEC HUS has an incidence of 20 per million population, most common affects children and can occur in localised outbreaks. STEC HUS accounts for 90% of HUS cases. The remaining cases, termed atypical HUS, are most commonly due to a defect in complement regulation leading to excessive activation and endothelial injury. A TMA can develop in response to a defined trigger including infection (HIV), drugs (anti-VEGF, calcineurin inhibitors, mitomycin, gemcitabine), after bone marrow transplantation or malignancy. HUS can also follow infection with *Streptococcus pneumonia* (pneumococcal HUS).

TMA occurring after a transplant can be complement mediated atypical HUS particularly if atypical HUS was the cause of ESKD, but can also be CNI toxicity or an infective or alloimmune process.

Clinical Presentation

TMAs and present with a range of symptoms and should be considered in any patient with unexplained anaemia [with fragmented red cells] and thrombocytopenia. Serum LDH can be elevated with low haptoglobin and negative coombs test. TTP typically presents with neurological involvement (>80%) but renal involvement is seen in 30% and systemic features including fever and other organ involvement (heart, pancreas) are common (25–50%). Very low platelet counts and raised inflammatory markers is typically evident. Without treatment TTP has a poor prognosis with a mortality of >50% which can occur rapidly (hours) after presentation.

Symptoms of STEC infection typically develop 3 days after infection with diarrhoea (bloody in 60%) and abdominal pain. This resolves after 5–7 days. Only about 15% of patients with STEC infection then go onto develop HUS. Anaemia can be severe and AKI is almost always present and 60% of patients require dialysis. Neurological involvement is reported in 20–50% of cases. Recovery occurs in most cases, although death can occur (<5%) and CKD and hypertension can develop.

Atypical HUS usually causes AKI but other organ involvement is common, including abdominal pain and diarrhoea. An environmental trigger (e.g. pregnancy) can be identified. The presentation of secondary forms of HUS will be defined by the underlying cause.

Differential Diagnosis

Other diseases that can present with features similar to a TMA with thrombocytopenia and MAHA include sepsis with disseminated intravascular coagulation (abnormal coagulation and low fibrinogen) and autoimmune disease particularly SLE and APS (prolonged PT and APL antibodies). Malignant hypertension, causing endothelial injury, can cause thrombocytopenia, MAHA and AKI and is difficult to differentiate from other causes of TMA which can cause hypertension.

Investigation and Management

It is important to diagnose a TMA in a patient as prompt initiation of treatment is important particularly for TTP. There are no reliable clinical features to distinguish between the causes of TMA although certain features, for example presence of bloody diarrhoea 1 week before presentation in a patient with STEC, will suggest the cause. The investigation and management of TMA are summarised (Fig. 13.1).

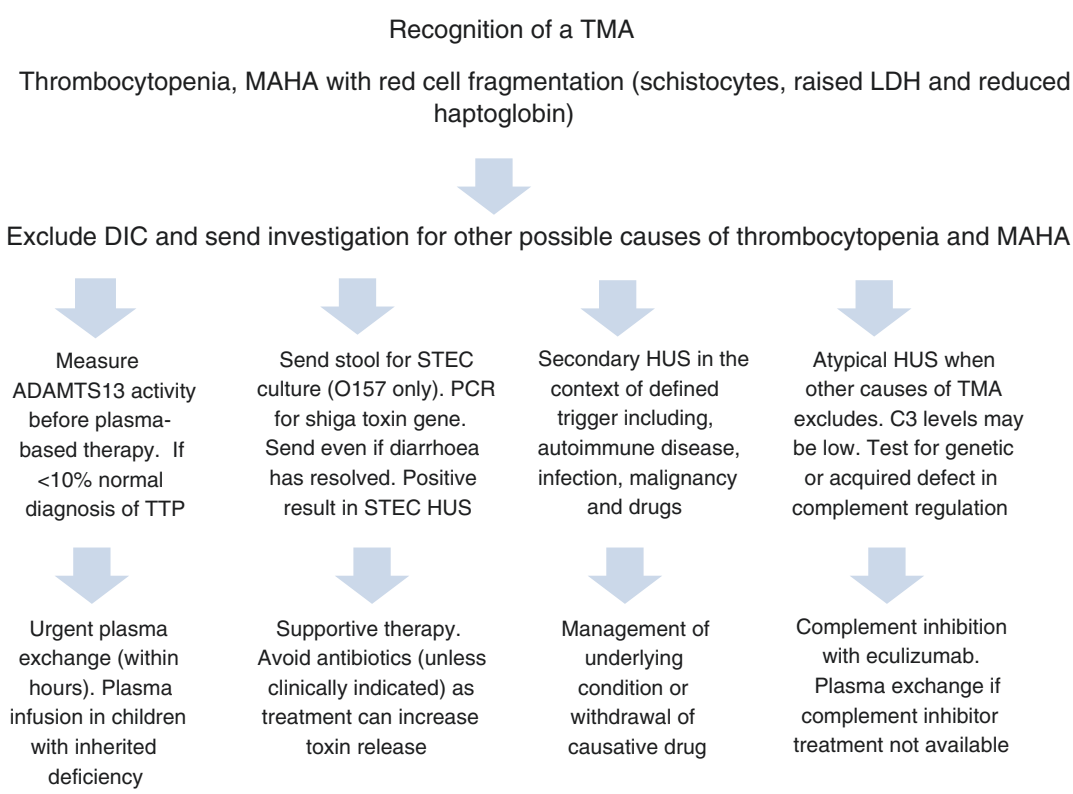

Fig. 13.1 Investigation and management of a TMA

Plasma exchange should be started as soon as the diagnosis of TMA is made until TTP has been excluded by assessing ADAMTS13 activity. The diagnosis of STEC HUS may be suggested by the history of colitic symptoms, but these are not always present (approximately 10%) and diarrhoea will usually have stopped by the time HUS develops. There may be evidence of an inflammatory response with high WCC and CRP. It is important to send stool for culture and PCR even if diarrhoea has stopped.

Atypical HUS is a diagnosis of exclusion and if suspected the patient should be assessed for abnormalities in complement regulation including genetic loss of function variants in complement factor H, factor I and CD46. Gain of function variants in the complement pathway proteins C3 and factor B can also occur. Approximately 10% (or higher in some countries) of cases of atypical HUS are due to acquired autoantibodies to factor H.

The management depends on the cause of TMA. TTP requires urgent plasma exchange which should be started until TTP has been excluded. Although, many different therapies have been tested in STEC HUS there is no evidence for anything other than supportive care including dialysis if required. Complement inhibition with eculizumab, if available, is effective in atypical HUS otherwise plasma exchange should be considered.

If a kidney biopsy is performed there is evidence of thrombi in the glomerular capillaries and small and medium sized arteries. Other features include mesangiolysis, microaneurysm formation and necrosis in blood vessel walls.

Practice Points

- Clinical assessment, including serological testing and kidney biopsy, are important to diagnose secondary glomerular diseases.
- Most secondary glomerular diseases are treatable. Treatment is determined by the diagnosis, severity of kidney involvement and extra-renal disease manifestations.
- Treatment will often involve a combination of drugs the use of which is associated with significant risk and therefore treatment should be supervised by an experienced clinician.
- Secondary glomerular diseases can relapse so long-term monitoring is important.

Conclusions

The presentation of secondary glomerulonephritis present with haematuria, proteinuria, increase creatinine and hypertension. Extrarenal features such as skin rash, joint pains, oral ulcers may be helpful like the 67-year-old man with ANCA-associated vasculitis. However the diagnosis largely depends on serological findings and kidney biopsy. Immunosuppressive treatment has improved outcomes over the last four decades. Better understanding of the pathophysiology and drug development has helped us with newer therapies.

Questions

1. In a patient who is diagnosed with PR3-ANCA associated with a GPA phenotype which of the following are correct:
   A. The PR3 ANCA detects proteinase 3 in a perinuclear distribution by immunofluorescence
   B. The risk of relapse after induction is lower than in a patient who is MPO-ANCA positive
   C. Higher cumulative dose of corticosteroids is associated with increased mortality
   D. C5aR inhibition can replace cyclophosphamide as part of the induction regime
   E. Rituximab is only indicated if induction with cyclophosphamide has been unsuccessful

Answer: C (Difficult)

A significant proportion of mortality in AAV is attributed to treatment. Lower doses of corticosteroids appear to be equally effective with a better side effect profile and associated with lower mortality rates. The other answers are incorrect.

2. In the clinical TMA clinical case which of the following is true:
   A. The presence of AKI excludes a diagnosis of TTP
   B. STEC HUS is unlikely because the diarrhoea has stopped
   C. STEC HUS can be excluded by a negative stool culture
   D. Close contacts should be screened for STEC infection
   E. STEC is likely so neurological disease will not occur

Answer: D (Difficult)

The likely diagnosis is STEC HUS. This can be passed from person to person and outbreaks can occur. Close household contacts should be screened. The presence of AKI does not exclude TTP, but the preceding history and age of the patient make TTP unlikely. STEC HUS typically develops after diarrhoea has stopped and neurological disease can occur. A negative culture does not exclude STEC HUS, particularly in the stool sample is sent after antibiotics. PCR is more sensitive and can remain positive when culture is negative.

3. For a 24 year woman with a new diagnosis of SLE, proteinuria (2 g/day), a Cr of 138 μmol/L and a kidney biopsy demonstrating Class IV LN which of the following treatment option should be advised:
   A. Pulse methylprednisolone followed by oral steroids
   B. Pulse methylprednisolone followed by oral steroids and azathioprine
   C. Pulse methylprednisolone followed by oral steroids and plasma exchange

D. Pulse methylprednisolone followed by oral steroids and MMF
E. Pulse methylprednisolone followed by oral steroids and oral cyclophosphamide

Answer: D (Easy)

The only first line treatment is steroids and MMF. Cyclophosphamide is given intravenously for the treatment of LN.

4. A 60-year-old man presented with a 5 day history of abdominal pain. He is drowsy and hypertensive (BP 188/108 mmHg) but otherwise examination was normal. He was anaemic (Hb 94 g/L) with a platelet count of 16×10^9/L. He has evidence of AKI with a Cr of 316 μmol/L. Which is the most important next step.
   A. Haemodialysis
   B. Plasma exchange
   C. Platelet transfusion
   D. Plasma infusion
   E. Blood pressure control

Answer: B (Easy)

This could be TTP with a reduced level of consciousness and very low platelet count. It is a medical emergency and should be treated urgently with plasma exchange until ADAMTS13 activity is known. In this age group an inhibitor of ADAMTS13 is more likely so plasma infusion is insufficient.

5. In the protein deposition clinical case which is the most likely diagnosis:
   A. AL amyloid due to a polyclonal plasma cell disorder
   B. AA amyloid due to an undiagnosed chronic infection
   C. AL amyloid due to an undiagnosed chronic infection
   D. AA amyloid due to monoclonal plasma cell disorder
   E. AL amyloid due to monoclonal plasma cell disorder

Answer: E (Easy)

AL amyloid is more likely that AA amyloid and is use to an abnormal plasma cell clone (not polyclonal). AA amyloid is associated with chronic infection.

6. In the cryoglobulinaemia clinical case the low level of C4 suggests:
   A. A likely association with SLE
   B. Activation of the alternative pathway of complement
   C. Reduced hepatic synthesis of C4 due to liver disease
   D. The presence of C1q binding immune complexes
   E. An underlying defect in complement regulation resulting in excessive activation

Answer: D (Difficult)

The formation of immune complexes in cryoglobulinaemis will activate the classical pathway of complement due to C1q binding the Fc position of IgG and IgM. This leads to the low C4 which is typically found in croglobulinaemia in the absence of any other autoimmune disease.

7. In which of the following protein deposition diseases is not associated with immunoglobulin fragment deposition:
   A. Light chain deposition disease
   B. AA Amyloid
   C. AL Amyoid
   D. Fibrillary glomerulonephritis
   E. Immunotactoid glomerulonephritis

Answer: B (Easy)

AA amyloid is due to deposition of Serum Amyloid A protein. The other diseases are due to deposition of immunoglobulin (or a fragment of immunoglobulin).

8. In the AAV case a biopsy was performed which showed a necrotising glomerulonephritis with crescents in 35% of glomeruli. Which of the following is the most appropriate treatment:
   A. High dose corticosteroids
   B. High dose corticosteroids and azathioprine
   C. High dose corticosteroids and cyclophosphamide
   D. High dose corticosteroids, cyclophosphamide and plasma exchange
   E. Delay immunosuppression because of concerns about infection

Answer: C (Easy)

The presence of fever raised white cell count and CRP are consistent with a diagnosis of vasculitis and should not delay treatment. A combination of corticosteroids with cyclophosphamide is the most appropriate treatment. There is no benefit of adding plasma exchange.

9. In the SLE clinical scenario which of the following statements about investigation is most appropriate:
   A. Provided kidney function does not decline further a biopsy is not required
   B. ANA titers are specific for a diagnosis of SLE
   C. Anti-Sm antibodies will be positive in most cases of lupus nephritis
   D. Low serum C3 concentration reflects urinary protein loss
   E. Anti-dsDNA antibody titres are associated with disease activity

Answer: E (difficult)

Anti dsDNa antibody titres do reflect disease activity. A kidney biopsy is required to assess class of lupus nephritis. ANA titres are found in a range of autoimmune disease unlike anti-Sm which is specific to SLE but only found in a minority of cases. Low C3 levels are due to complement activation and consumption.

10. In a patient with mixed croglobulinaemia which antibodies could be found in the precipitate from serum on cooling:
    A. Monoclonal IgM binding polyclonal IgG
    B. Polyclonal IgG binding monoclonal IgM
    C. Polyclonal IgM binding to monoclonal IgG
    D. Polyclonal IgG binding monoclonal IgG
    E. Monoclonal IgM binding monoclonal IgM

Answer: A (Difficult)

In most cases of mixed cryoglobulinaemia type 2 a monoclonal immunoglobulin (usually IgM) with Rheumatoid factor activity will bind to polyclonal IgG and IgM.

Test your learning and check your understanding of this book's contents: use the "Springer Nature Flashcards" app to access questions using https://www.sn.pub/cz9Cok. To use the app, please follow the instructions in Chap. 1.

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