REVIEW

Cryoglobulinaemic vasculitis: classification and clinical and therapeutic aspects

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Cryoglobulinaemia may cause cutaneous vasculitis and glomerulonephritis, potentially leading to end stage renal failure. An important proportion of cryoglobulinaemias are secondary to hepatitis C virus infection. Emerging antiviral treatment options offer a chance for causal therapy of these cases of cryoglobulinaemia. This review summarises the classification and clinical and therapeutic aspects of cryoglobulinaemic vasculitis and glomerulonephritis.

The manifestations of small vessel vasculitides are often protean and may involve both the skin and internal organs, including the kidney. To avoid potentially life-threatening complications, correct differential diagnosis and exclusion of internal organ involvement are particularly important. Previously, cryoglobulinaemic vasculitides were assumed to be primary or essential. It has now become evident that the majority of cryoglobulinaemic vasculitides are secondary manifestations of other diseases, especially of viral origin, such as chronic hepatitis C virus (HCV). This recognition offers an opportunity for causal rather than symptomatic therapy of these vasculitides. The different causes, types and complications of cryoglobulinaemic vasculitis, including glomerulonephritis, are reviewed here.

DEFINITIONS AND CLASSIFICATIONS

Cryoglobulins are cold-precipitable immunoglobulins from serum. Cryoglobulinaemia remains asymptomatic in most cases but can lead to immune complex tissue deposition, causing cryoglobulinaemic vasculitis. Based on the classification introduced in 1974,[1] three main and one additional[2] categories of cryoglobulins are currently recognised (table 1).

Cryoglobulinaemic vasculitis belongs to the large group of cutaneous vasculitides that originate from inflammation in the small or medium sized vasculature (the so-called small vessel vasculitides), leading to clinically apparent skin lesions, and in some cases also to internal organ involvement.[6] Vasculitis can be classified using clinical (tissues and vasculature presumed to be involved on clinical grounds), histopathological (tissues and vessels involved, type of vascular destruction) or immunopathological (identified molecular pathogenesis) terms, or their combination.[6–8] The most widely used classification today is that coined by the Chapel Hill consensus conference which is mainly based on anatomical distinctions of the dominant vessels affected (table 2).[8]

For the clinician, establishing the hypothesis that a patient may have small vessel cutaneous vasculitis is the first step. From a pathogenetic point of view, the largest group of small vessel dermal vasculitides consists of the immune complex mediated types.[6–8] These include mainly cryoglobulinaemic vasculitis, Henoch–Schönlein purpura, urticaria vasculitis and vasculitis associated with malignancy (see table 2 for details).

Vasculitis affecting not only the small but also medium sized vessels includes the so-called pauci-immune forms (table 3).[8] Other disorders causing cutaneous vasculitis include the following: inflammatory bowel disease, Behçet's disease and septic emboli, as in bacterial endocarditis, and EED (erythema elevatum diutinum), an immune complex vasculitis of unknown aetiology.[6] It may be associated with HIV infection and usually presents with symmetrically distributed purple plaques and nodules on the extensor surfaces.[13 14]

PATHOGENESIS/AETIOLOGY

Type II and III (mixed) cryoglobulinaemia is strongly associated with HCV infection, and since the first reports[15] the causative role of HCV is now widely acknowledged.[4 16] The presence of cryoglobulins increases with duration of HCV infection; 30–50% of HCV positive patients have mixed cryoglobulins while in selected patients with chronic HCV infection, cryoglobulins are found in 55–90% of cases.[17–19] Rheumatoid factor is positive in most patients with chronic HCV infection.[18] Type II cryoglobulinaemia is more strongly associated with HCV than type III cryoglobulinaemia (that is, 90% and 70%, respectively).[12] An association of cryoglobulinaemia with chronic hepatitis B virus (HBV) infection has been suggested but is highly questionable as the prevalence of cryoglobulins in HBV infected patients is similar to that in other chronic liver diseases.[17] At best, approximately 2% of mixed cryoglobulinaemic vasculitides seem to be attributable to HBV infection, according to one study.[20]

Type III cryoglobulins have been reported to occur as a transient phenomenon in many different infections.[4] It is thought that partially uncontrolled B cell clone proliferation, which can often be detected in patients with long standing HCV infection, underlies the formation of mixed

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Abbreviations: ANCA, antineutrophil cytoplasmic antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; MPGN, membranoproliferative glomerulonephritis

Table 1 Types of cryoglobulinaemia, composition of cryoprecipitates and associated diseases[1 2]

Type of cryoglobulinaemia (estimated frequency[3])	Composition of cryoprecipitates	Associated or underlying diseases
Type I (25%)	Monoclonal IgM (sometimes IgG, IgA)	Lymphoproliferative diseases, plasma cell dyscrasias, multiple myeloma, Waldenström's macroglobulinaemia, MGUS
Type II* (25%)	Combination of monoclonal (usually IgM) and polyclonal (usually IgG)	HCV infection
Type III* (50%)	Polyclonal Igs	HCV infection, connective tissue diseases
Type II–III (frequency unknown)	Oligoclonal IgM	HCV infection, other infections, autoimmune diseases, lymphoproliferative diseases, chronic liver disease, proliferative glomerulonephritis

HCV, hepatitis C virus; MGUS, monoclonal gammopathy of undetermined significance.
*Type II and III cryoglobulinaemias are classically referred to as ''mixed cryoglobulinaemias'' because of their polyclonal component. Type II–III is an intermediate state between the entirely polyclonal type III and the monoclonal, polyclonal type II. Some authors presume a continuous transition from a purely polyclonal composition to a partially monoclonal component by a process of successive clonal selection.[2 4 5] The monoclonal IgM components usually have rheumatoid factor activity—that is, they bind to the Fc portion of IgG leading to immune complex formation.

Table 2 Types of vasculitis according to the dominant vessels affected, as defined by the Chapel Hill consensus conference[8]

Dominant vessels affected	Type of vasculitis (pathomechanism)	Specific diagnostic hallmarks
Small vessels	Cutaneous leucocytoclastic angiitis (unknown aetiology, drug induced/allergic)	Eventual drug history (possible serum IgE elevation), absence of cryoglobulins or IgA on histology, negative immune serology
	Henoch-Schönlein purpura (IgA deposition)	Increased serum IgA, usually normal serum complement, tissue IgA deposition, especially in paediatric patients, triggered by infections,[9–11] clinical triad or tetrad of purpura, arthralgia, gastrointestinal symptoms and renal failure[2 12]
	Mixed cryoglobulinaemia (cryoglobulin deposition)	Serum cryoglobulins, often low serum C4, tissue deposition of cryoglobulin and complement
Small to medium vessels	Wegner's granulomatosis (mostly ANCA associated)	ANCA, renal and nasopharyngeal involvement
	Churg–Strauss syndrome (mostly ANCA associated, eosinophilia)	ANCA, eosinophilia
	Microscopic polyangiitis (mostly ANCA associated)	ANCA
Medium vessels	Polyarteritis nodosa	Clinically medium vessel affection with negative immune serology
	Kawasaki syndrome (unknown)	ESR acceleration, C-reactive protein increased
Large vessels	Temporal arteritis (unknown)	ESR acceleration, C-reactive protein increased
	Takayasu arteritis (unknown)	ESR acceleration

ANCA, antineutrophil cytoplasmic antibody; ESR, erythrocyte sedimentation rate.

Table 3 Pauci-immune forms of vasculitis[8]

- Wegener's granulomatosis
- Churg–Strauss syndrome
- Drug induced ANCA associated vasculitis
- Microscopic polyangiitis and polyarteriitis nodosa
- Connective tissue disease associated vasculitis
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjögren's syndrome

ANCA, antineutrophil cytoplasmic antibody.

Table 4 Frequent associations of mixed cryoglobulins[4 22]

- Infections
  - HIV, bacterial endocarditis
- Collagen vascular diseases
  - Sjögren's syndrome
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Dermatomyositis/polymyositis
- B cell non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia

The aetiologies of cryoglobulinaemia were found to be 75% infectious, 24% autoimmune and 6% neoplastic in one study.[23]

Table 5 Clinical and serological findings in patients with cryoglobulinaemic vasculitis[4]

	Frequency (%)
Clinical	
Purpura	50–100
Arthralgias, weakness	>70
Combination of purpura/arthralgia/weakness*	<40
Polyneuropathy	40–70
Raynaud's phenomenon	20
Secondary Sjögren's syndrome†	
CNS involvement	
Gastrointestinal involvement	
Renal involvement	
Serological	
Anti-HCV-antibodies	90
Detectable HCV RNA	85
Hypocomplementaemia (ie, C4)	90
Elevated rheumatoid factor	70–100
Antinuclear antibodies (ANAs)	20
Antismooth muscle antibodies	20–25
Antiphospholipid antibodies	5–20
ANCAs	<5

ANCA, antineutrophil cytoplasmic antibody; HCV, hepatitis C virus.
*So-called cryoglobulinaemic vasculitis syndrome.
†SS-A-/SS-B antibody negative.

cryoglobulins.[16 21] Indeed, HCV is also a lymphotropic virus and it is worth noting that 6–28% of patients with type II cryoglobulinaemia develop symptomatic lymphoma after 4–10 years of follow-up.[6 21]

Importantly, non-viral liver disease (for example, due to alcohol abuse or immunological autoimmune hepatitis) has also been associated with increased rates of mixed cryoglobulin formation.[17] Other associations of mixed cryoglobulins are summarised in table 4.

MANIFESTATIONS OF CRYOGLOBULINAEMIC VASCULITIS AND CLINICAL APPROACH

Between 2% and 15% of cryoglobulin positive patients are considered to develop cryoglobulinaemic vasculitis.[6 24] Frequent symptoms and serological findings are listed in table 5. An important first diagnostic step is detection of serum cryoglobulins. For correct detection, blood samples must be constantly kept at 37°C on the way to the laboratory. Cold precipitation can be Ca^{++} dependent and may take up to a week, as described previously.[2 25] Encountered cryoglobulin levels range from as low as 0.05 g/l to 10 g/l and sometimes higher, depending on the type of cryoglobulin and the laboratory.[1 2 26] Standard detection uses immunoelectrophoresis and immunofixation; the more sensitive methods for detection of oligoclonal components of type III cryoglobulins are immunoblotting and two dimensional electrophoresis.[4] Cryoprecipitates may deplete HCV antibody and HCV antigens from serum, leading to a false negative hepatitis serology. This can be overcome by paired testing from both the serum and cryoprecipitate.[4]

DERMATOLOGICAL SYMPTOMS AND SIGNS

The clinical hallmark of cutaneous vasculitis is palpable purpura that usually occurs in the lower extremities. Possible manifestations of purpura are: (i) multiple small papules covering larger skin areas (fig 1A, from a patient with cutaneous small vessel vasculitis); (ii) larger confluent necrotising lesions (fig 1B, from a patient with polyarteriitis nodosa); and (iii) livedo racemosa, marble-like changes to the skin that

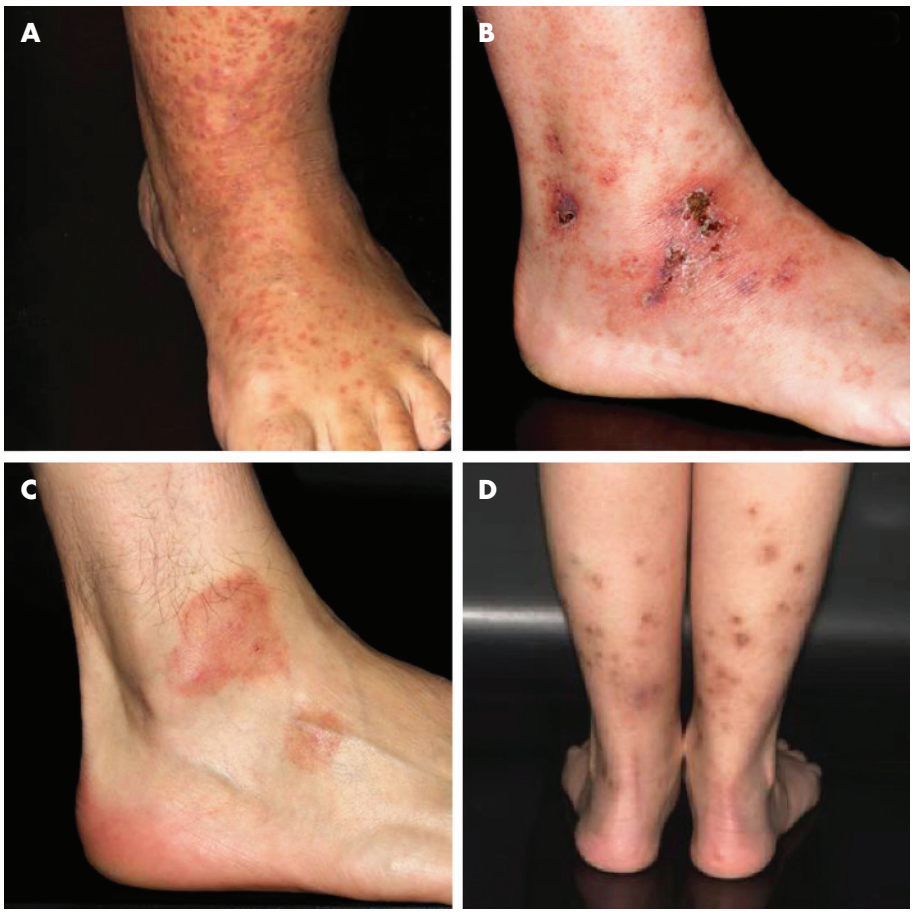

Figure 1 Skin lesions relevant for the differential diagnosis of cutaneous vasculitis. (A) Papular lesions in a vasculitis marked by leucocytoclastic vasculitis on histology. (B) Polyarteriitis nodosa with papular necrosis and livedo racemosa-like colouring of the skin. (C) Epidermal oedema seen in urticaria. (D) Prurigo simplex. Itching papular lesions.

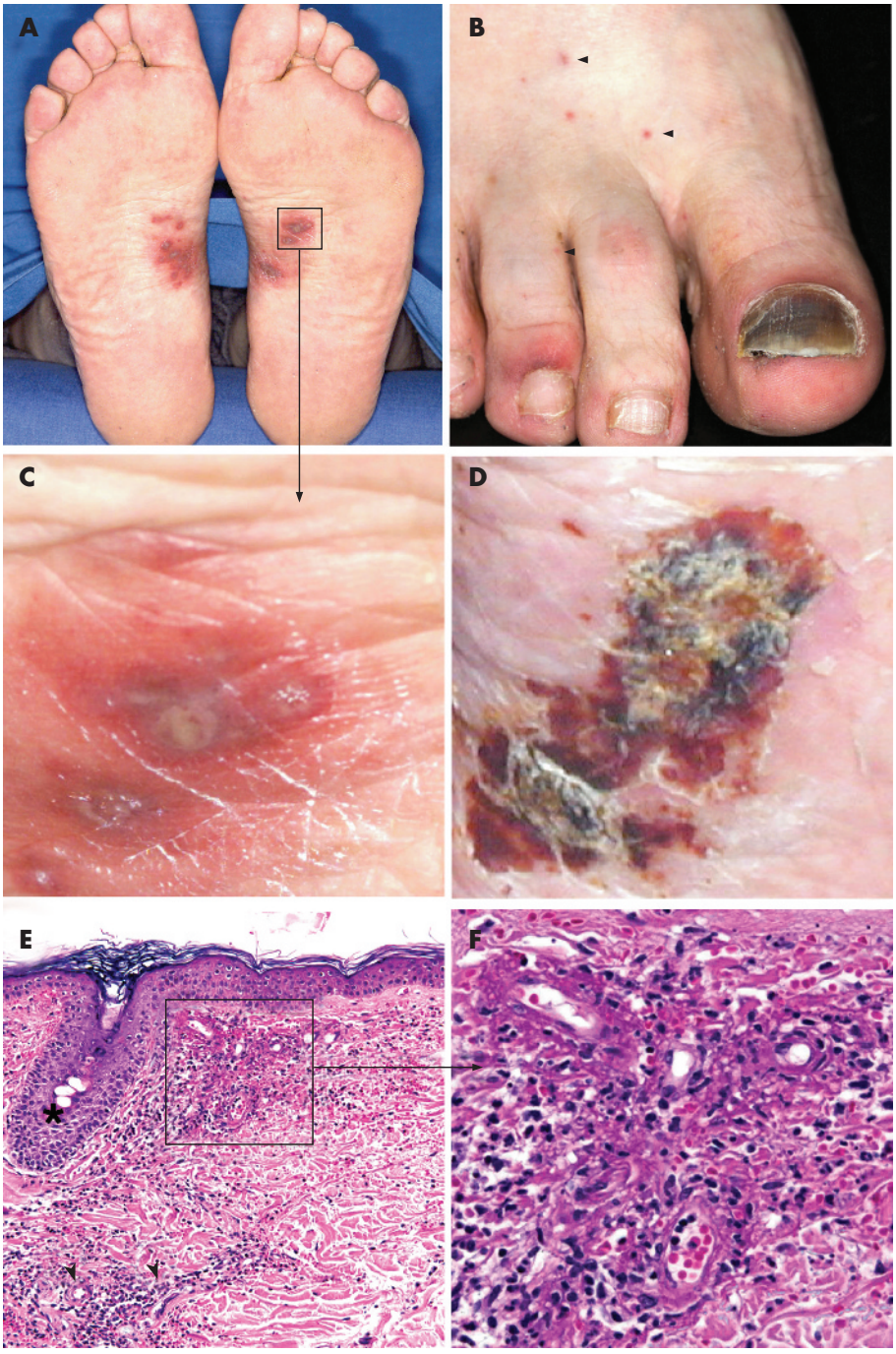

Figure 2 Dermal findings in a patient with type II cryoglobulinaemia associated with chronic alcoholic liver disease in the absence of viral hepatitis. (A) Symmetrical purpuric papular lesions on the medial aspect of the foot soles and (B) petechial macular lesions on the dorsal aspect of the foot on presentation. (C) Magnification of the boxed area from (A). (D) Partial healing of the foot sole lesion after 8 weeks of oral steroid treatment. (E) Skin biopsy from the leg, vertical section. Biopsy confirmed the presence of vasculitis by showing infiltration of the perivasculature with leucocytes and cell dust (so-called leucocytoclastic histopathological pattern). From top to bottom: stratum corneum, normal epidermis circumscribing a hair follicle (indicated by asterisk), dermis. Two vascular regions exhibiting wall thickening and extravasation of cells are highlighted by the box and arrowheads, respectively (haematoxylin-eosin stain, magnification 100×). (F) Magnification of the boxed area from (E). Note vascular wall thickening and extravascular accumulation of leucocyte nuclei and cell dust (haematoxylin-eosin stain, magnification 300×). Presence of type III cryoglobulin in the absence of other pathological immune serologies or evidence of neoplasm or internal organ involvement confirmed the diagnosis of isolated dermal cryoglobulinaemic vasculitis.

are mostly present in necrotising vasculitides (fig 1B). These patterns may occur singularly, serially or in conjunction, and they are not specific to the type of vasculitis, thus precluding a diagnosis on clinical grounds alone. Furthermore, vasculitis of the skin must be differentiated from an array of non-vasculitic lesions mimicking its aspect that include plain urticaria, which denotes a non-vasculitic itchy oedema of multiple or idiopathic origin (fig 1C), prurigo simplex, showing itchy papular lesions of a generally benign nature that may be associated with liver disease, diabetes and paraneoplasia (fig 1D),[27] or from erythema multiforme (not shown). Figure 2 depicts findings from a patient with cryoglobulinaemic vasculitis. Early necrotic lesions at the medial foot sole can be seen (fig 2A, C) which developed into late necrosis after several weeks of corticosteroid treatment (fig 2D). In addition, small macular necrotic lesions can be seen (fig 2B). Necrosis of the toes has also been described with cryoglobulinaemic vasculitis (not shown).

To secure the diagnosis, a skin biopsy is always required to define the histopathology, to search for deposition of immune complexes and complement, and for the exclusion of non-vasculitic cutaneous conditions such as pigmented purpuric eruptions, scurvy, atheroembolic or thrombotic disease that may clinically mimic vasculitis.[6 28] Figure 2E and 2F show the histopathological pattern of leucocytoclastic vasculitis in the patient with cryoglobulinaemic vasculitis. Leucocytoclasis

Table 6 Association of cryoglobulinaemic vasculitis with kidney disease

Cryoglobulinaemia	Frequency	Associated kidney disease	Pathogenesis	Reference
Type I	Usually not Rare	Glomerulonephritis Tubular damage (Fanconi syndrome), depositions in the GBM and mesangium	 Plasma cell dyscrasia-associated light chain and amyloid depositions	Hent[30] Kumar[31]
Type II	Most common (~75%)	Glomerulonephritis: MPGN I* (~85%) Mesangioproliferative GN (~7%)	Fibronectin specific monoclonal IgM leading to glomerular leucocyte attraction and damage	Johnson,[12 33] Fornasieri[32] Roccatello[53]
Type III	Much less common (~25%)	Glomerulonephritis: MPGN I* (~85%) Mesangioproliferative GN (~7%)	Unknown, possibly like cryoglobulinaemia type II	Johnson,[12 33] Fabrizi,[34] Beddhu [35] Roccatello[53]

GN, glomerulonephritis; GBM, glomerular basement membrane; MPGN, membranoproliferative glomerulonephritis.
*Almost invariably associated with hepatitis C virus (HCV) infection. Cryoglobulins in the absence of HCV infection are only rarely associated with MPGN I.[34 36]

denotes the presence of leucocytic vascular/perivascular infiltrates and leucocytic cell dust.[6 28] However, such a pattern in haematoxylin-eosin stained specimens is seen in almost all vasculitides, independent of aetiology.[6 28] Only additional analysis for subtypes of deposited immune complexes and possible complement allow for further aetiological differentiation.

A complete vasculitis workup should also include fundoscopy[29] and a comprehensive panel of immune serologies. Investigations searching for infections and neoplasms may also be necessary to establish the type and aetiology of the vasculitis, as well as the degree of extradermal organ involvement.[6 28]

RENAL COMPLICATIONS

All three main types of cryoglobulinaemic vasculitis can lead to kidney disease, as summarized in table 6. In brief, membranoproliferative glomerulonephritis (MPGN) type I is typical. Up to 10–30% of patients with chronic HCV infection develop MPGN I. Very recently, 146 patients with cryoglobulinaemic vasculitis-associated renal disease from Italy were studied. The mean-age was 52 years, 87% of patients were found to be infected with HCV (98% genotypes 1b and 2), ~85% had MPGN I and ~7% had mesangioproliferative glomerulonephritis on renal biopsy.[53] Generally, cryoglobulin associated MPGN I can present with either proteinuria (41%), the nephritic syndrome (21%), the nephritic syndrome (14%; marked by urinary erythrocyte acanthosis, fig 3), and both chronic (12%) and acute (9%) renal failure.[12 33 36 53] Extrarenal symptoms such as skin involvement may be absent in 30–80% of cases.[37 53] On histology MPGN I exhibits subendothelial deposition of cryoglobulin immune complexes and often complement c3 in the glomerular basement membrane. Because of subsequent mesangial cell proliferation, there is marked thickening of the glomerular basement membrane and glomerular hypercellularity (fig 4).

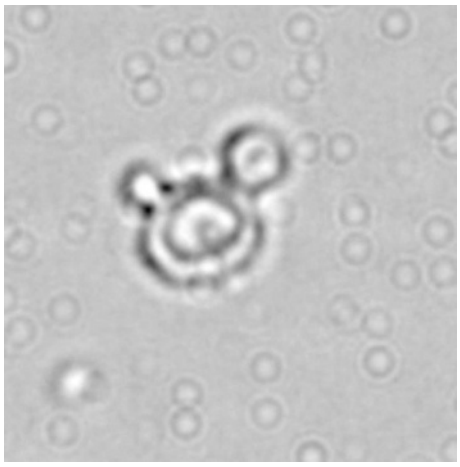

Figure 3 Urinary acanthocyte, a dysmorphic erythrocyte with abnormal membrane blebs, indicating glomerular haematuria.

TREATMENT OF CRYOGLOBULINAEMIC VASCULITIS

Asymptomatic cryoglobulinaemia merits no treatment. Therapy of secondary cryoglobulinaemic vasculitis is aimed at the primary disease, as summarised in table 7. For HCV associated cryoglobulinaemic vasculitis type II, antiviral strategies aiming at cure of HCV infection, as outlined in table 7, have been shown to be clearly superior to conventional immunosuppression.[46] However, some controversy remains concerning the effectiveness of anti-HCV treatment in patients with active cryoglobulinaemic vasculitis.[47] Recently, an entirely new approach of treating cryoglobulinaemic vasculitis by direct blockage of complement C5 has been suggested and has been demonstrated to be effective in a mouse model.[48] This finding is of potential interest for future treatment strategies in humans.

PROGNOSIS

The prognosis of mixed cryoglobulinaemic vasculitis is benign in 50% of cases. However, one third of cases are reported to have a moderate to severe course, particularly because of renal and/or hepatic insufficiency. Consequently, 10 year survival rates are significantly lower than in the normal population.[20] According to recent data from small patient numbers, antiviral treatment may cure or control HCV associated mixed cryoglobulinaemic vasculitis and possibly improve prognosis.[38] In previous studies, the survival of MPGN I patients not stratified for aetiology was significantly lower than in the normal population: 50% of patients progressed to end stage renal disease (ESRD) within 10 years and the recurrence rate in patients with renal transplants was 30–70%. A number of recent small studies have reported successful MPGN I treatment using antiviral strategies (see table 7). Further large studies and follow-up data are needed to determine the benefit of HCV treatment on the course of both cryoglobulinaemic vasculitis and MPGN I. The topic is of importance as MPGN I is a major cause of glomerulonephritis all over the world.[49] The prognosis of cryoglobulinaemia with no identified underlying disease (essential mixed cryoglobulinaemia) is not well known, and renal involvement is associated with a poor prognosis (renal failure in 10% of patients).[50] However, recently a potentially promising therapeutic approach using the CD-20 antibody rituximab has been suggested.[38]

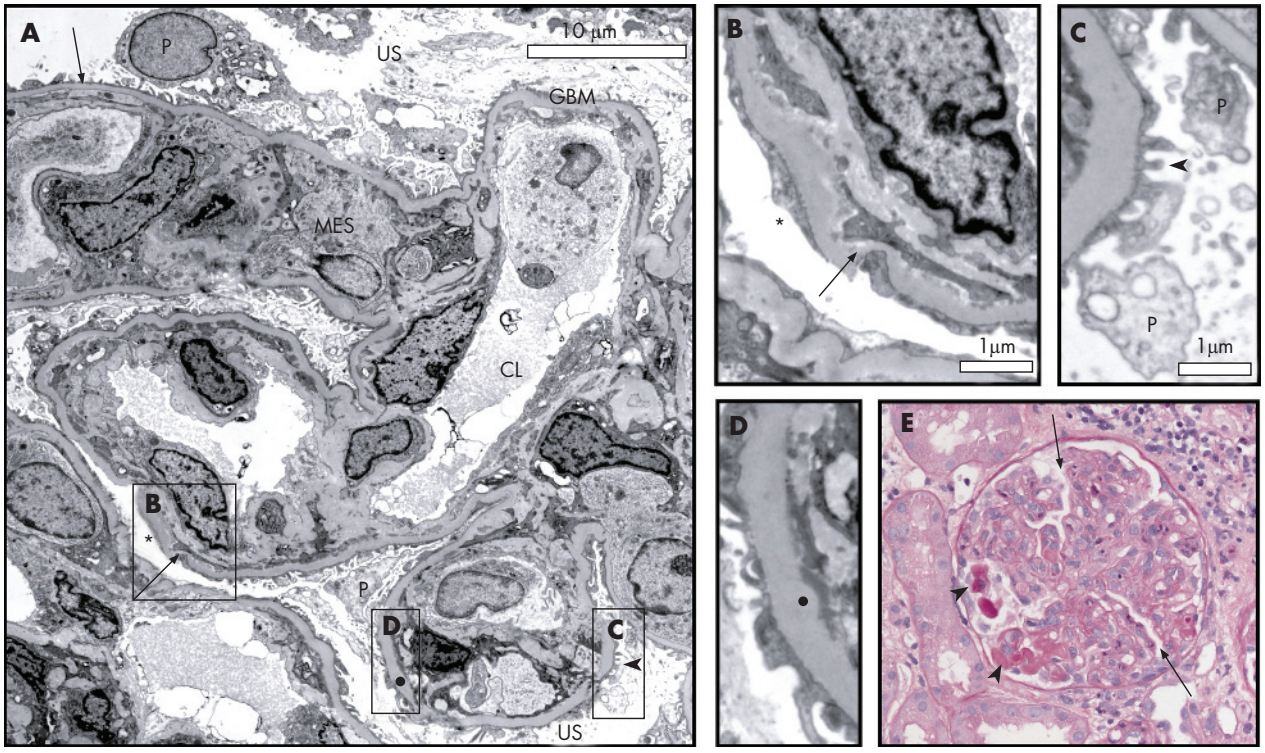

Figure 4 Renal biopsy samples of membranoproliferative glomerulonephritis (MPGN) type I. CL, capillary lumen; US, urinary space; MES, cell proliferation in mesangium; P, podocytes; GBM, glomerular basement membrane. (A) Electron microscopy showing subendothelial and mesangial electron dense immune deposits (●), an increase in cells in the mesangium and segmental duplication of the glomerular basement membrane (arrows). Foot processes of podocytes are partially maintained (arrowheads) and partially not preserved (asterisk). Boxes indicate areas magnified in (B–D), respectively. (B) Doubling of the GBM (arrow) and loss of podocyte foot processes (asterisk). (C) Preserved podocyte foot processes (arrowhead) and cross sections of large podocyte processes (P). (D) Subendothelial electron dense immune deposits (●). (E) Light microscopy, periodic acid–Schiff staining (magnification 200×). The glomerulus appears lobulated (arrows), hypercellular and with increased mesangial matrix. Individual capillary loops are occluded by homogenous hyalinous material (arrowheads). Silver stains can also be performed, to discern the double contour of the thickened GBM on light microscopy, also referred to as ''tramtrack'' sign (not shown). Immunofluorescence techniques provide molecular proof of immunoglobulin and possibly complement deposition within the GBM (not shown).

CONCLUSIONS AND PERSPECTIVE

In recent years, considerable progress has been made in the availability of routine diagnosis and epidemiological study of hepatitis C infection, clearly demonstrating its association with cryoglobulinaemia of types II and III. The concept that chronic HCV infection underlies the majority of cases of cryoglobulinaemia is now widely acknowledged. On average, HCV infected patients develop cryoglobulinaemia in 30–50% of cases and MPGN type I in 10–30% of cases. Up to 2–15% of patients with cryoglobulinaemia develop overt cryoglobulinaemic vasculitis. Treatment should be directed towards aetiology rather than symptomatic. HCV infection, as the most common possible underlying condition, has to be excluded in every case. Experience with and data on antiviral treatment options have grown considerably in recent years. A 48 week course of combined peginterferon and ribavirin represents the current gold standard of anti-HCV therapy.

Teaching points

(1) Cutaneous vasculitis is diagnosed by combining laboratory analysis and histology, including staining for immunoglobulin and complement deposits.
(2) Type I cryoglobulinaemia usually results from paraproteinaemic neoplasm eventually leading to myeloma kidney and, very rarely, glomerulonephritis.
(3) Type II and III (''mixed'') cryoglobulinaemias result mostly from hepatitis C virus (HCV) infection and in this association can cause glomerulonephritis, especially membranoproliferative glomerulonephritis (MPGN) I. Up to 10–30% of patients with longstanding HCV infection develop glomerulonephritis. 70–90% of MPGN I cases are associated with HCV and type II cryoglobulins. Type II cryoglobulinaemia is also associated with HIV infection, liver disease and lymphoma. Type III cryoglobulinaemia causes renal disease less often.

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Recommended further reading

(i) on cryoglobulinaemic vasculitis[38]
(ii) on recent aspects and treatment of HCV infection[38 39 51 54]
(iii) on membranoproliferative glomerulonephritis[52 53]
(iv) on cutaneous vasculitis[6]

Table 7 Treatment of cryoglobulinaemic vasculitis (CV) with and without renal involvement

CV type and treatment	Comment	Reference
HCV associated CV type I		
Directed against primary disease (eg, specific therapy for multiple myeloma)		
HCV associated CV type II		
*PEG-ylated IFNα + ribavirin	Current standard of care for HCV elimination	Ferri,[38] Dienstag,[39] Strader[40]
IFN-α2b	100% HCV elimination in patients with early infection	Wiegand[41]
IFN-α + ribavirin	Treatment studies in patients with CV and MPGN I. HCV elimination leads to improvement of CV and MPGN I	Sabry,[42] Bruchfeld[43]
Immunosuppression using rituximab (anti-CD 20 antibody)	Successful treatment of CV with renal involvement (no HCV elimination)	Roccatello[44]
Initial high dose adjuvant immunosuppression and/or plasma exchange	Warranted in severe cases of CV/renal involvement before antiviral or rituximab treatment are effective	Cacoub[45]
Essential CV (ie, CV with no known underlying cause)		
Immunosuppression using glucocorticoids	Controls minor signs but does not prevent disease progression	Lamprecht,[4] Fiorentino,[6] Cacoub[45]
Immunosuppression using methotrexate or azathioprine	Established treatment regimens	Lamprecht[4]
Immunosuppression using rituximab (anti-CD 20 antibody)	New strategy	Ferri,[38] Roccatello[44]
Cyclophosphamide, Fauci scheme, plasma exchange	Recommended for treating severe cases of CV and CV with renal involvement	Lamprecht[4]
Colchicine, ciclosporin, melphalan, intravenous immunoglobulin, low antigen diet	Second-line treatment regimens that have also been suggested by some authors	Fiorentino[6]

HCV, hepatitis C virus; IFN, interferon; MPGN, membranoproliferative glomerulonephritis.
Rituximab is contraindicated or must be used with caution in patients with renal failure.
Antiviral treatment is not routinely recommended for patients with the following: hepatic decompensation, severe uncontrolled psychiatric disorder or severe cytopenia. Rituximab is contraindicated or must be used cautiously in patients with renal failure. Positive predictors for response to antiviral therapy include: genotypes 2 or 3, low HCV RNA levels, age ⩽40 years, absence of liver cirrhosis/bridging fibrosis/steatosis, lighter body weight and non-black ethnicity.[38 39] In renal involvement with proteinuria, symptomatic treatment with angiotensin-converting enzyme inhibitors, angiotensinreceptor blockers and diuretics is generally advised.[54]

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