The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Non-ANCA-associated vasculitides

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1 Introduction

In general, vasculitides are divided according to their manifestation in different vessel beds. Apart from ANCA-associated vasculitides, cryoglobulinaemic vasculitis, Henoch-Schoenlein purpura, cutaneous leukocytoclastic vasculitis and secondary vasculitides due to rheumatoid arthritis, systemic lupus erythematosus (SLE) or Sjögren's Syndrome comprise the group of small vessel vasculitides. In polyarteri-

Table 1. Classification criteria of large vessel-vasculitides.

	American College of Rheumatology Criteria	**Chapel Hill Consensus Conference Criteria**
Takayasu's Arteritis	Age < 40 years Claudication of extremities Decreased brachial artery pulse Blood pressure difference > 10 mm Hg Bruit over arteries Arteriogram abnormality	Granulomatous arteritis of aorta and its major branches *Usually occurs in patients younger than 50 years.*
Temporal Arteritis/ Giant Cell Arteritis	Age > 50 years New headache Temporal artery tenderness Increased ESR > 50 mm/h Abnormal artery biopsy: vasculitis with a predominance of mononuclear or granulomatous inflammation	Granulomatous arteritis of aorta and its major branches, with a predilection for the extra cranial branches of the carotid artery *Usually occurs in patients older than 50 years and is often associated with polymyalgia rheumatica.*

Table 2. Classification criteria of panarteritis nodosa.

	American College of Rheumatology Criteria	Chapel Hill Consensus Conference Criteria
Polyarteritis nodosa	Weight loss Livedo reticularis Testicular pain or tenderness Myalgia, weakness or leg tenderness Mono- or polyneuropathy Diastolic blood pressure > 90 mmHg urea > 40mg/dl or creatinine > 1.5 mg/dl Hepatitis B virus Arteriographic abnormality (aneurysms or occlusion of the visceral arteries) Biopsy of medium size vessel (small or medium sized artery) containing PMN	Necrotizing inflammation of medium-sized or small arteries without glomerulonpehritis or vasculitis in arterioles, capillaries or venules

Table 3. Classification criteria of non-ANCA associated small vessel vasculitides.

	American College of Rheumatology Criteria	Chapel Hill Consensus Conference Criteria
Cryoglobulinaemic Vasculitis	No criteria	Vasculitis, with cryoglobulin immune deposits, affecting small vessels and associated with cryoglobulins in serum
Henoch-Schönlein pupura	Palpable purpura Bowel angina Age at onset < 20 years Biopsy showing granulocytes in the walls or arteries and venules	Vasculitis, with IgA-dominant immune deposits, affecting small vessels
Cutaneous Leucocytoclastic Vasculitis	No criteria	Isolated cutaneous leucocytoclastic angiitis without systemic vasculitis

tis nodosa, medium-size vessels are involved, whereas the large-vessel vasculitides are represented by giant cell arteritis and Takayasu's arteritis. Classification criteria of the vasculitides are given in Tables 1–3, Fig. 1.

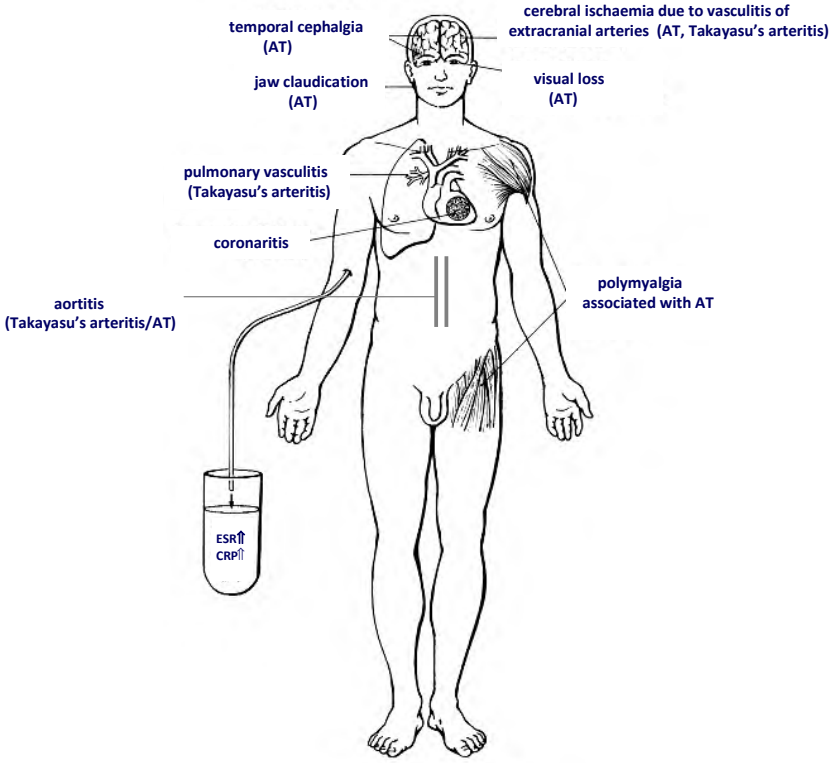

Figure 1. Clinical manifestations of temporal arteritis and Takayasu's arteritis.

Table 4. Signs and symptoms of GCA/arteritis temporalis.

Symptoms of GCA/AT	Frequency (%)
Cephalgia	>95%
Visual disturbance	30%
Visual loss	10–15%
Jaw claudication	
Fever	10–15%
Aortitis	10–15%

Table 5. Signs and symptoms of Takayasu's arteritis (TA).

Symptoms of TA	Frequency (%)
Diminished or absent pulses	85–95%
Vascular bruits	80–95%
Hypertension (renal)	30–80%
Retinopathy	up to 40%
Aortic regurgitation due to dilatation of aorta	20%
Pulmonary artery involvement	15–100%

Large-vessel vasculitides are characterised by ischaemic symptoms due to stenosis or occlusion of these vessels [1] (Tables 4 and 5). In giant cell arteritis (GCA), temporal arteritis is the typical manifestation, leading to sudden and severe temporal cephalgia. Visual loss may also occur (in around 10 to 15 % of patients) and is usually due to vasculitis of the posterior ciliary artery and subsequent anterior ischaemic opticus neuropathy [1, 2]. Temporal arteritis/GCA is often associated with polymyalgia rheumatica (PMR), which is characterised by severe, proximal myalgia, but PMR also occurs alone. Apart from the temporal artery, other large vessels such as the aorta or brachial/femoral arteries may also be affected and then may lead to claudication of the extremities, which is a hallmark not only of GCA but of Takayasu's arteritis (TA) [1, 2]. TA is a disease of younger people (aged less than 40 years) and tends to follow a more aggressive course. Complications of TA include renal artery stenosis, angina abdominalis

Table 6. Signs and symptoms of panarteritis nodosa.

Symptoms of Panarteriitis	Frequency (%)
Weight loss, fever, night sweats	>70%
Polyneuropathy	60%
Renal involvement (malignant hypertension, renal artery stenosis)	40–60%
Gastrointestinal involvement (abdominal pain, aneurysmal bleeding)	40%
Skin involvement (livedo, subcutaneous nodules, purpura, digital ischaemia/gangrene)	40%
Arthralgia/myalgia; each:	30%
CNS-involvement (encephalopathy, infarcts, subarachnoidal haemorrhage due to aneurysmal bleeding)	20%

due to mesenteric ischaemia, coronary arteritis, aortic regurgitation and pulmonary arteritis. Most frequently affected arteries are the subclavian arteries, the left carotid artery and the abdominal aorta [1, 2]. Temporal arteritis most frequently occurs in Northern Europeans (15–25/100 000/yr), whereas Takayasu's arteritis predominates in Japanese and southeast Asians and rarely occurs in western countries (incidence: 2.6/Mill/yr in North America). There is a female predominance in both GCA (female/male: 4 : 1) and TA (female: male 9 : 1). The female predominance in TA is reported to be lower in Western countries [1, 2].

The typical features of polyarteritis nodosa are aneurysms and/or stenosis of the visceral arteries due to vasculitis of medium-size vessels [3] (Table 6, Fig. 2). Gastrointestinal vasculitis may lead to bowel ischaemia or bleeding. Other vasculitis manifestations include polyneuropathy, vasculitis of skeletal muscles, stenosis of the renal arteries with subsequent hypertension, digital ischaemia/gangrene and CNS involvement. Polyarteriitis nodosa is strongly associated with hepatitis B, especially in countries where this viral infection is common. Its incidence is markedly

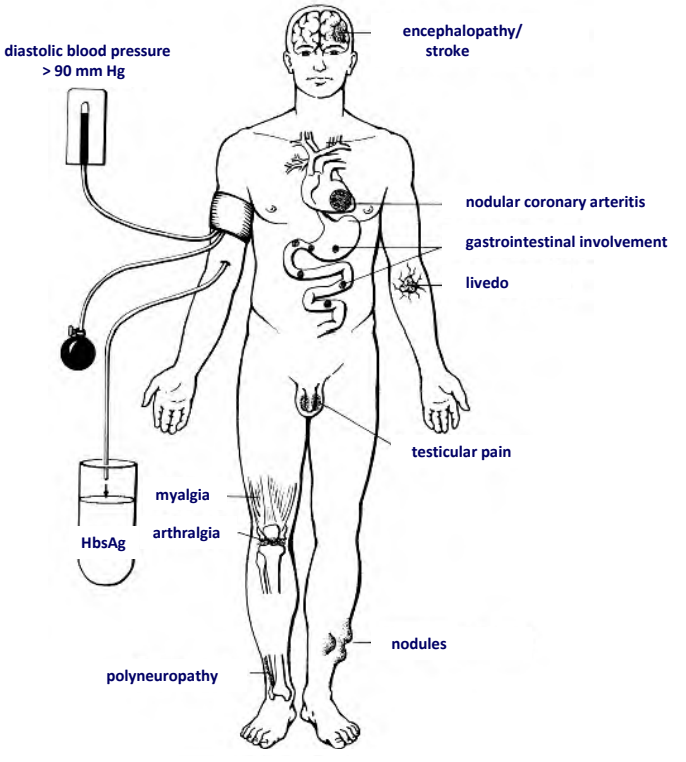

Figure 2. Clinical manifestations of polyarteritis nodosa.

higher in an Alaskan Eskimo population with a hyperendaemia for hepatitis B compared to European countries (77/Mill/yr compared to 0.2–34/Mill/yr). Importantly, panarteritis nodosa does, by definition, not affect small vessels, whereas in several small vessel-vasculitides, involvement of medium-size vessels is found (e.g. in granulomatosis with polyangiitis (formerly Wegener's Granulomatosis), microscopic polyarteritis).

In cryoglobulinemic vasculitis (CV), small vessels of skin (purpura), peripheral nerves (polyneuropathy) and kidney (membranoproliferative glomerulonephritis) are frequently affected [4] (Table 7, Fig. 3). CV is strongly associated with hepatitis C infection, especially in Mediterranean countries; if no underlying cause is found, "essential" CV is diagnosed. The definite incidence and prevalence of CV is not known, but is supposed to be higher in Southern Europe compared to Northern Europe and the US. In Southern Europe, 86 % of patients with CV show hepatitis C viraemia and 5 % of patients suffering from hepatitis C virus infection develop CV [4].

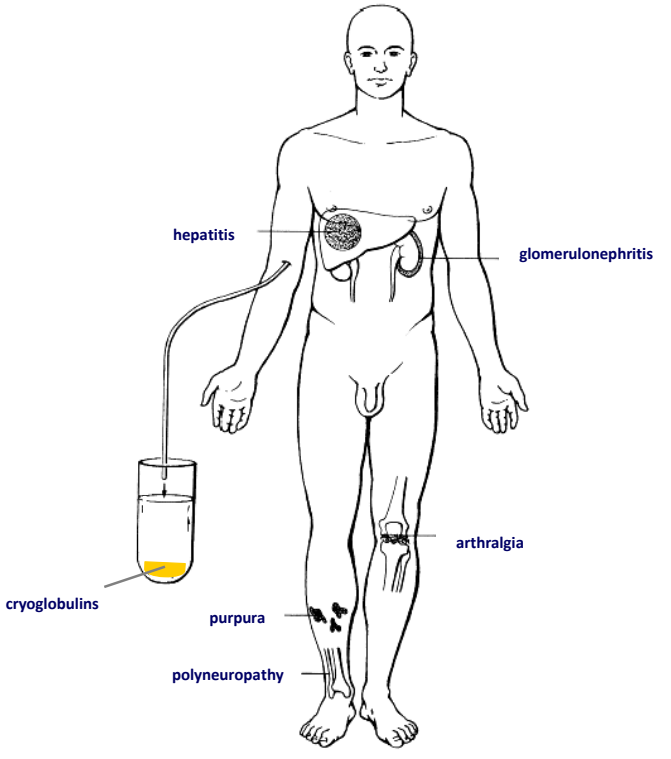

Figure 3. Clinical manifestations of cryoglobulinaemic vasculitis.

Table 7. Signs and symptoms of cyroglobulinaemic vasculitis (CV).

Symptoms of CV	Frequency (%)
Purpura	98%
Weakness	100%
Arthralgia	98%
Polyneuropathy	80%
Raynaud's phenomenon	50%
Hepatopathy	80%
Renal involvement	30%

Henoch-Schoenlein purpura (HSP) mainly occurs in children (incidence 135–180/Mill/yr) and rarely in adults (incidence 13/Mill/yr) and is characterised by cutaneous vasculitis (purpura) with IgA immune complex deposits in the tissue and a decrease of serum complement proteins [5] (Table 8, Fig. 4). HSP may be complicated by renal and gastrointestinal involvement (mesangioproliferative glomerulonephritis, gastrointestinal bleeding due to erosions and ulcers). Prognosis is worse in adults than in children due to a higher frequency of renal involvement. Typically, initial macrohaematuria with subsequent microhaematuria is present in renal involvement. Infections and vaccination are under discussion as triggering factors for HSP.

In disorders such as RA and SLE, secondary vasculitis can occur. In both of these disorders, secondary vasculitis may be due to cryoglobulins. Small vessel vasculitis in RA and SLE predominantly affects skin (purpura) and peripheral nerves (polyneuropathy). In SLE diffuse alveolar haemorrhage due to pulmonary capillaritis and CNS vasculitis has also been described.

Table 8. Signs and symptoms of Henoch-Schönlein pupura (HSP).

Symptoms of PSH	Frequency (%)
Purpura	>90%
Arthralgia/arthritis	70%
Gastrointestinal involvement	70%
(abdominal pain, nausea, haematemesis, intestinal bleeding)	
Renal involvement	20-80%

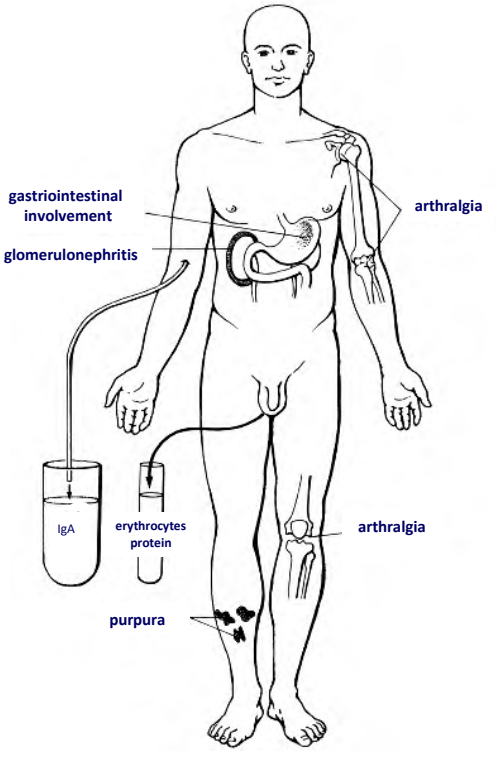

Figure 4. Clinical manifestations of Henoch-Schönlein pupura.

2 Diagnostic procedures for experts

Routine diagnostic procedures in large vessel vasculitis include palpation of arterial pulses, auscultation of large vessels and assessment of arterial blood pressure. When temporal arteritis is suspected, ultrasound of the temporal artery or cranial high-resolution MRI should be performed to search for inflammation of the vessel wall depicting itself as hypo-ecchogenic "halo". A temporal biopsy should be sought to confirm the diagnosis. Large vessel vasculitis of aorta and arteries of the extremities is detected by MR-angiography and PET (positron emission tomogram) The former visualizes wall oedema and stenosis, the latter shows an enhanced glucose uptake at sites of an inflammatory process, however, both methods have not been thoroughly validated yet for patients under treatment. In polyarteritis, angiography is also frequently used to assess aneuryms and/or stenosis. If possible, a biopsy specimen should be obtained (e. g. muscle biopsy).

The work-up in small vessel vasculitides depends on the suspected organ involvement, e.g. assessment of renal function (urinalysis, creatinine clearance, proteinuria), or neurological evaluation (EMG, ENG). A biopsy should be performed at first presentation to confirm the diagnosis (e.g. biopsy of skin, kidney, skeletal muscle or nervus suralis).

In general, serological markers of inflammation such as ESR and CRP are elevated and represent some of the items in some of the vasculitis classification criteria (e.g. in GCA). There is no specific marker (e.g. an autoantibody) in large vessel vasculitis and polyarteritis; serum should be tested for cryoglobulins, when CV is suspected, and the type of cryoglobulin needs to be assessed if cryoglobulins are detected. CV is characterised by the occurrence of a type II (or sometimes type III) cryoglobulinaemia (Tables 1, 7). The patient should be screened for underlying diseases inducing cryoglobulins such as infections (hepatitis C) and autoimmune disorders (RA, SLE, Sjögren's syndrome). As CV and HSP are immune complex diseases, complement proteins are usually decreased. In polyarteritis, hepatitis B serology needs to be obtained. Serum IgA levels may be elevated in HSP.

3 Requirements for family practitioners

In cases of high acute phase reactants and acute temporal cephalgia in patients aged over 50 years, the suspicion of temporal arteritis must be raised. Claudication of extremities, angina abdominalis, stroke or myocardial infarction in young people in conjunction with high acute phase reactants is highly suspicious of Takayasu's arteritis.

Medium and small-vessel vasculitides affect multiple organs and may be more difficult to recognize. Weight loss, fever, arthralgia, high acute phase reactants are common but very unspecific signs of medium- and small-vessel vasculitides. Livedo, purpura, myalgia, polyneuropathy, gastrointestinal bleeding or impaired kidney function may represent signs of an underlying vasculitis in patients with elevated acute-phase reactants.

If any of the diseases are suspected, the patient should be referred to a rheumatologist/rheumatology or internal medicine unit immediately.

4 Follow up

Patients require immunosuppressive therapy for several years or for life. Patients remain at risk for relapse or opportunistic infections such as CMV reactivation or *Pneumocystis jirovecii*-pneumonia. In some patients, irreversible organ damage occurs if immunosuppressive therapy is introduced too late (e.g. persistent visual loss in temporal arteritis, persistent polyneuropathy or requirement for haemodialysis due to renal insufficiency).

Patients need to be assessed for signs and symptoms of disease activity on a regular basis by the family practitioner (ideally monthly) and by the rheumatologist (every three months when the disease is stable). Acute phase reactants such as ESR and CRP should also be tested regularly (monthly when the disease is stable). Furthermore, immunosuppressive therapy needs surveillance of certain laboratory parameters as suggested by the specialist (see chapter ANCA-associated vasculitides). In some cases, image guided techniques or other technical diagnostic procedures are needed to document follow-up (e.g. MR-angiography), but may not be validated.

Follow-up laboratory tests (such as cryoglobulins, hepatitis viral load or complement proteins) will be carried out by the specialist.

5 Management

Therapy of the vasculitides is adapted according to organ involvement and activity of the disease. Recently, recommendations for the management of small and medium-size vessel vasculitis [6] and large vessel vasculitis [7] have been published by the EULAR (European League Against Rheumatism, Table 9).

In large vessel vasculitis, the early introduction of glucocorticoids is recommended for the induction or remission. Initially, prednisolone should be administered at doses of 1 mg/kg/day and maintained for a month. In case of (early) visual loss, higher doses of glucocorticoids or methylprednisolone pulses may be considered. Adjunctive immunosuppressive therapy is usually needed to control TA (e.g. cyclophosphamide in severe disease and methotrexate (MTX) or azathioprine for less severe disease or maintenance). MTX may also be used in temporal arteritis/GCA for glucocorticoid-sparing. Furthermore, GCA patients should receive low-dose aspirin to avoid arterial occlusion. Arterial reconstruction or bypass-grafting may be needed, especially in TA, but should be performed when the disease is in remission.

Hepatitis B-associated polyarteritis requires antiviral therapy in conjunction with glucocorticoids. Additional plasmapheresis is highly successful in the induction of remission. In non-hepatitis B associated polyarteritis, immunosuppressants such as cyclophosphamide may be used for the induction of remission in organ-threatening disease; MTX is an option in non-organ threatening disease or as maintenance therapy.

CV is treated according to the underlying condition. Anti-viral therapy with ribavirin and interferon-alpha is primarily recommended for hepatitis C-associated CV, whereas essential CV is treated by immunosuppressive therapy in the same way as the other small vessel vasculitides (see chapter ANCA-associated vasculitides). In cases of organ threatening CV, immunosuppressive therapy is introduced in spite of high viral load to reduce organ damage induced by vasculitis, and antiviral therapy is commenced when vasculitis activity is under control. Im-

Table 9. Treatment recommendations for non-ANCA-associated vasculitides according to EULAR/EUVAS.

Vasculitis	Recommended therapy
Large vessel vasculitis	Remission induction: - high-dose glucocorticoids (1mg/kg/day) for 1 month - consider additional immunosuppressant as adjunctive therapy Early visual loss: - consider high dose i.v. methylprednisolone Maintenance therapy: - no recommendation - immunosuppressive therapy is usually needed long-term Additional therapy: - aspirin in GCA - reconstructive surgery in TA when disease is in remission
Panarteritis nodosa	Hepatitis B-associated: - GC + antiviral therapy + plasma separation Non-Hepatitis-associated: - no recommendation - immunosuppressive therapy needed
Cryoglobulinemic vasculitis (CV)	Hepatitis-C-associated CV: - antiviral therapy essential CV: - treat like other small vessel vasculitides rituximab may be an option in HCV-associated and non-viral CV consider plasma separation in life-threatening disease

munosuppressive therapy is then discontinued or switched to a less toxic agent. Furthermore, rituximab may be an option in hepatitis C-associated and non-hepatitis-C associated CV and should be considered when cyclophosphamide is not successful or contraindicated [8]. It may be useful to combine rituximab with antiviral therapy. Plasmapheresis has been of benefit in life-threatening disease.

6 Diagnostic tests

The non-ANCA associated vasculitides are not associated with typical autoantibody profiles. ESR and CRP serve to assess disease activity; in CV and HSP, the decrease of complement may be an additional marker for disease activity.

If CV is suspected, cryoglobulins in serum should be measured and the type of cryoglobulins should be assessed. The patient needs to be tested for hepatitis B and/or C if polyarteritis or CV is diagnosed. In secondary vasculitis, testing for autoantibodies of the underlying disease is necessary (e.g. determination of rheumatoid factor (RF) and anti-CCP-antibodies in rheumatoid arthritis or measurement of antinuclear antibodies (ANA), anti-ds-DNA antibodies and extractable nuclear antibodies (ENA) in connective tissue diseases.

7 Testing methods

Cryoglobulins

Cryoglobulins precipitate in the cold and redissolve on re-warming. To test for cryoglobulins, blood needs to be drawn into a pre-warmed syringe in the absence of anticoagulants. Serum is removed after centrifugation and kept at 4° Celsius for 2–3 days. Cryoglobulins of type I tend to precipitate within 24 hours, whereas cryoglobulins of type III may need up to 7 days to precipitate (Fig. 5). To assess the cryocrit (volume of precipitate as a percentage of original serum volume) the precipitated sample is centrifuged again. The concentration of cryoglobulins can

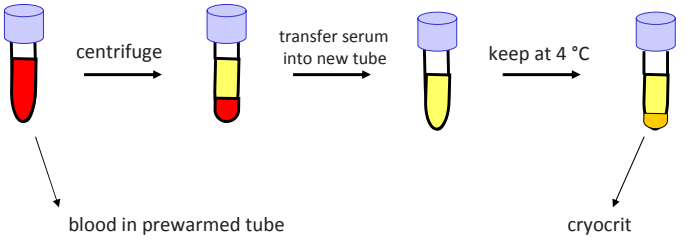

Figure 5. Determination of cryocrit.

be determined by spectophotometric analysis. The type of cryoglobulinaemia is specified by immunological assays assessing different cryoglobulin components.

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