

Non-Infectious Cryoglobulinemia Vasculitis (CryoVas): Update on Clinical and Therapeutic Approach

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Abstract CryoVas is a small vessel vasculitis associated with the presence of circulating cryoglobulins. In the absence of HCV infection, several disorders have been identified in association of CryoVas. Although evidence is limited, a few studies have recently described the clinical presentation, prognosis, and therapeutic management of non-infectious CryoVas. Patients with type I CryoVas, especially associated with hematologic malignancies, have shown a worse clinical presentation. Recent studies have also identified prognostic factors in mixed CryoVas. Therapeutic management in non-infectious CryoVas remains to be defined. Overall, treatment options should be individualized based on severity of involvement. In this setting, new data have emerged regarding the role of biologic therapy in non-infectious CryoVas. Off-label use of rituximab should be highlighted, based on the assessment of benefits and risks, especially infections.

Keywords Cryoglobulinemia · Vasculitis · Non-infectious · Autoimmune diseases · Hematologic malignancies · Idiopathic cryoglobulinemia · Prognosis · Treatment · Rituximab · Therapy

Introduction

The term cryoglobulinemia vasculitis (CryoVas) represents a small-medium vessel vasculitis affecting predominantly skin,

joints, peripheral nervous system, and kidneys [1•]. In the context of clinical symptoms suggestive of CryoVas, the most important finding is the detection of cryoglobulins in serum. Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures below 4 °C, and dissolved after rewarming at 37 °C [2].

Brouet et al. [3] have proposed a classification based on the clonality and type of immunoglobulins. Type I cryoglobulins consist of single monoclonal immunoglobulins, either IgM or IgG. Type II cryoglobulins consist of polyclonal IgG with monoclonal IgM with rheumatoid factor activity. Type III cryoglobulins are a mixture of polyclonal IgG and IgM with rheumatoid factor activity. Type II and III are often referred to as mixed cryoglobulinemia. Since the discovery of hepatitis C virus (HCV) infection in the late 1980s, it has become clear that HCV represents the most common cause (80 %) of CryoVas [4, 5], being predominantly associated with type II mixed cryoglobulinemia. However, CryoVas has also been associated with other infections, as well as autoimmune diseases and hematologic malignancies. In addition, when no etiologic factor can be identified, CryoVas is defined as idiopathic or essential [6••].

CryoVas may cause clinical manifestations due to two major mechanisms. Hyperviscosity and vascular occlusion is more frequent in type I cryoglobulinemia, usually associated with high levels of serum cryoglobulins [7]. On the other hand, mixed cryoglobulinemia (type II) is associated with formation and deposition of immune-complexes, primarily affecting small and medium vessels [8].

Most data available regarding disease expression, outcomes, follow-up, and treatment options in CryoVas series have focused on HCV-associated cryoglobulinemia. In this review, we aim at describing the clinical presentation, prognostic factors, and treatment options available in patients with non-infectious CryoVas.

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Non-Infectious Causes

A variety of clinical disorders have been described in association with CryoVas (Table 1).

Autoimmune Diseases

Patients with systemic autoimmune diseases can present with complications of mixed cryoglobulinemia. In this setting, primary Sjögren's syndrome is the most common rheumatic disease associated with cryoglobulinemia, especially in those patients exhibiting extraglandular manifestations. Detection of cryoglobulins in Sjögren's patients has also been identified as predictive factor for B-cell lymphoma [9, 10]. Cryoglobulins have been reported, although in lower percentages, in other autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE). In a large cross-sectional study including 122 SLE patients, cryoglobulins were found in nearly 25 % of patients. Hepatitis C virus (HCV) infection was only detected in 21 % of patients with cryoglobulinemia. Of interest, patients with a cryocrit greater than 1 % showed a higher frequency of HCV infection than those with a cryocrit less than or equal to 1 %. Only cutaneous vasculitis was more common in SLE patients with than in those without cryoglobulins [11].

Neoplasias

B-cell lymphoproliferative disorders are the major cause of cryoglobulinemia associated with malignancy. Type I

cryoglobulinemia accounts for nearly 10–15 % of patients [12], and mostly linked with multiple myeloma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, and B-cell non-Hodgkin lymphoma [13]. Rarely, cryoglobulins have also been identified in patients with solid neoplasias.

Essential or Idiopathic

Once different causes have been ruled out, CryoVas is considered as idiopathic or essential (nearly 25 % of patients in HCV-negative series) [5]. It should be noted that cryoglobulinemia, as such, is a laboratory finding sometimes not necessarily associated with any clinical manifestation. Several factors have been associated with the development of CryoVas symptomatology, including age, underlying disease, type (especially type II subclass), and high levels of cryoglobulins [4].

Clinical Manifestations

Most studies available in the literature on CryoVas came from series including HCV-associated CryoVas patients. Data on clinical features have also been described extensively for the different types of cryoglobulinemia. We will focus specifically on clinical manifestations from the latest published series on non-infectious mixed CryoVas and type I CryoVas. Table 2 highlights differential features between infectious and non-infectious CryoVas.

Table 1 Non-infectious causes associated with CryoVas

Etiology	Frequency	Cryoglobulins	Diagnosis
Autoimmune diseases	10–15 %	Mixed Type II-III	<ul style="list-style-type: none"> • Sjögren's syndrome • Systemic lupus erythematosus • Rheumatoid arthritis Less frequent: Systemic sclerosis, polyarteritis nodosa, giant-cell arteritis, Takayasu's arteritis, ANCA-associated vasculitis, inflammatory myopathies, antiphospholipid syndrome, AOSD
Neoplasias	10–15 %	Mostly type I	B-cell lymphoproliferative disorders: <ul style="list-style-type: none"> • Multiple myeloma • Waldenström's macroglobulinemia • B-cell lymphoma • MGUS Less frequent: Myelodysplasia, Hodgkin's lymphoma, hairy cell leukemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, lung adenocarcinoma, renal cell carcinoma, hepatocellular carcinoma, papillary thyroid cancer
Essential-idiopathic	10 %	Type II	

ANCA antineutrophil cytoplasmatic antibodies; AOSD Adult-onset Still's disease; MGUS monoclonal gammopathy of unknown significance

(Adapted from Ramos-Casals et al. [6••])

Table 2 Differential features between infectious and non-infectious CryoVas

	Infectious CryoVas	Non-infectious CryoVas
Etiology	HCV (90 %) – HBV – HIV	<ul style="list-style-type: none"> • Autoimmune diseases: (SS – SLE – RA) • Hematologic malignancies: (MM, WM, B-cell lymphoma) • Essential/idiopathic
Cryoglobulins	Mixed (type II)	<ul style="list-style-type: none"> • Type I • Mixed (type II–III)
Pathogenesis	Immune complex-mediated Cryoprecipitation	<ul style="list-style-type: none"> • Hyperviscosity (type I) • Immune-complex mediated (type II–III)
Clinical findings	Small–medium vessel vasculitis	<ul style="list-style-type: none"> • Hyperviscosity syndrome (type I) • Small-medium vessel vasculitis (type II–III)
Laboratory	Type II cryoglobulins RF (+) – C3↓ – C4↓ ELISA Ab (+) HCV-RNA (serum – cryoprecit)	<ul style="list-style-type: none"> • Type I (SPEP) – M protein • ANA (+) – ENA (+)
Prognosis	Depending on: <ul style="list-style-type: none"> • Extension and severity 	<ul style="list-style-type: none"> • Depending on severity and underlying disease • Essential MC more aggressive • Type I: Depending on hematologic malignancies
Treatment	Depending on: <ul style="list-style-type: none"> • Extension and severity Vasculitis syndrome: <ul style="list-style-type: none"> • Corticosteroids • Immunosuppressants • Plasmapheresis • Rituximab • HCV: Antivirals, interferon 	Depending on: <ul style="list-style-type: none"> • Etiology and severity Vasculitis syndrome: (similar to CryoVas) <ul style="list-style-type: none"> • Rituximab controversial • Hyperviscosity • Plasmapheresis Underlying disorder: <ul style="list-style-type: none"> • Autoimmune diseases • Hematologic neoplasia

HCV hepatitis C infection; *HBV* hepatitis B infection; *HIV* human immunodeficiency virus; *SS* sjögren’s syndrome; *SLE* systemic lupus erythematosus; *RA* rheumatoid arthritis; *MM* multiple myeloma; *WM* waldenström’s macroglobulinemia; *RF* rheumatoid factor; *C3* complement fraction 3; *C4* complement fraction 4; *ELISA* enzyme-linked immunoabsorbent assay; *RNA* ribonucleic acid; *SPEP* serum protein electrophoresis; *ANA* antinuclear antibodies; *ENA* extractable nuclear antigens

Non-Infectious Mixed CryoVas

Mixed type II–III cryoglobulins are associated with clinical manifestations typical for small–medium vessel vasculitis. Mixed CryoVas is the result of immune-complex deposits, predominantly in the capillaries, venules, or arterioles. Disease expression is variable, ranging from mild symptoms to life-threatening complications. Skin is the most frequently involved organ, presenting as palpable purpura, ulcers, Raynaud’s phenomenon and acrocyanosis. Renal involvement is usually described as type I membranoproliferative glomerulonephritis. Neurologic manifestations include peripheral neuropathy, mostly sensory-motor mononeuritis multiplex.

A French group has recently published the largest series of non-infectious CryoVas patients. The French multicenter CryoVas survey was designed to describe the clinical presentation, prognostic factors, and treatment efficacy in patients with non-HCV CryoVas. Data including 242 patients showed some differential features between HCV-positive and -

negative CryoVas patients. Compared with type III mixed CryoVas, patients with non-infectious type II CryoVas had higher cryoglobulins levels, lower complement levels, and more frequent palpable purpura, peripheral neuropathy, and renal involvement [14••]. As compared with essential mixed CryoVas, connective tissue disease-associated CryoVas patients were predominantly younger women, who had more peripheral neurologic involvement, and less renal involvement.

Type-I CryoVas

In type I cryoglobulinemia, most clinical manifestations are secondary to hyperviscosity syndrome, with cryoglobulin precipitation and vascular occlusion as major pathogenic mechanisms involved. Vascular occlusion is more common in type I CryoVas, although systemic vasculitis may also occur. Clinical symptoms include acrocyanosis, Raynaud’s phenomenon, gangrene, and livedoreticularis. Neurologic (headache, confusion), ocular (blurry vision, visual loss), and rhino-

otological (hearing loss, epistaxis) manifestations have also been described [15].

Data on type I CryoVas are scarce in the literature as most published series have focused on mixed CryoVas patients. A survey from the French study group on CryoVas has been recently reported [16•]. Data from 64 cases of type I CryoVas were included: 28 patients with monoclonal gammopathy of unknown significance (MGUS) and 36 with hematologic malignancy. Demographics features (e.g., age at the time of diagnosis and predominance of females) were in keeping with those usually observed in HCV- and non-HCV-related mixed CryoVas. The study revealed that the major clinical manifestations were severe cutaneous involvement (necrosis and ulcers) in almost half the patients, associated with high levels of serum cryoglobulins. It should be noted that frequency of glomerulonephritis (20 %) was lower than reported in previous series. In contrast to what was expected, no clinical manifestation of hyperviscosity syndrome was found in the entire cohort. Finally, type I CryoVas was mostly associated with B-cell lymphoproliferative diseases, confirming the need to systematically screened these patients for an underlying B-cell malignancy.

Prognosis

Disease expression in CryoVas is variable, ranging from mild clinical manifestations to fulminant life-threatening complications (especially glomerulonephritis and systemic vasculitis). Prognosis is mostly influenced by cryoglobulinemic damage to vital organs and by underlying diseases and comorbidities.

Non-Infectious Mixed CryoVas

Evidence on the prognosis of non-infectious mixed CryoVas in the era of HCV screening is limited. Recently, the French multicenter and retrospective CryoVas survey have identified prognostic factors and survival rates in the largest cohort ($n=242$) of patients with non-infectious mixed CryoVas so far published in the literature [17•]. After a median follow-up of 35 months, 17 % of patients died, with severe infections (50 %) and vasculitis flare (19 %) as major causes of death. Survival rates were 91 % (1 year) to 65 % (10 years). A prognostic score, the CryoVas score (CVS), for the prediction of survival at 5 years was devised from this study. At diagnosis of vasculitis, pulmonary and gastrointestinal manifestations, renal failure (glomerular filtration rate less than 60 ml/min), and age (older than 65 years) were independently associated with poor outcomes and death.

In contrast, causes of death in HCV-related mixed CryoVas have been described mainly associated with end-stage liver disease and serious infections, but not vasculitic manifestations [18].

Type I CryoVas

Data on the prognosis of type I CryoVas are also lacking. Despite the lack of the evidence, type I CryoVas is considered a life-threatening disease, due to the severity of cutaneous and renal involvement and the prognosis of the underlying hematological disorder. The study from the French CryoVas survey analyzed patients with type I CryoVas. The 1-, 3-, 5-, and 10-year survival rates were 97, 94, 94, and 87 %, respectively. It should be noted that type I CryoVas related to hematological malignancy tended to be associated with a poorer prognosis as compared with MGUS. In this setting, all patients who died had hematologic malignancy, including Waldenstrom's macroglobulinemia in 3 patients and multiple myeloma in 1 patient.

Therapeutic Management

In general, therapeutic approach in CryoVas patients should be tailored according to the severity of clinical manifestations, etiopathogenic mechanism(s) involved (vasculitis vs. hyperviscosity syndrome) and the associated underlying disorders.

With the discovery of HCV infection as the main cause of CryoVas, most of the research has focused on the safety and efficacy of antivirals and interferon-alpha regimens. Evidence on the clinical spectrum and therapeutic options in non-infectious CryoVas patients is limited. Treatment options have been derived mainly from strategies used in HCV-CryoVas.

Non-Infectious Mixed CryoVas

Treatment options in patients with mild–moderate disease may include resting, avoidance of cold temperatures, nonsteroidal-antiinflammatory drugs (NSAIDs), and colchicine. In cases of severe or life-threatening manifestations, therapy is based on a combination of corticosteroids, immunosuppressants, plasmapheresis, and rituximab (RTX). The approach is empiric, as no clinical trial has previously studied these agents in CryoVas.

First line therapy may include:

- **Corticosteroids** (moderate-severe manifestations): methylprednisolone (0.5–1 g/day) for 3 days, followed by prednisone 1 mg/kg daily. When disease control is achieved, steroids should be tapered down.
- **Cyclophosphamide** (severe cases): oral (2 mg/kg daily) or intermittent IV (750 mg/m² monthly)

For remission maintenance, regimens include azathioprine (2 mg/kg daily) or mycophenolate mofetil (1 g twice daily).

The most promising biological approach of CryoVas used thus far is B-cell depletion with RTX. The rationale for this approach is that peripheral B-cell depletion should lead to a reduction in the B-cell clones that produce cryoglobulins.

To date, only two studies have addressed the role of RTX in non-infectious CryoVas. The first come from a prospective clinical data, including patients from the French Autoimmunity and Rituximab (AIR) registry [19]. The objective was to evaluate safety and efficacy of RTX in off-trial, real-life patients with non-viral CryoVas (Dosis: 375 mg/m²×4). RTX indication was due to refractory disease (75 %) and as first line therapy (25 %). The registry included 23 patients: primary SS (9), essential mixed CryoVas (8), and patients with an underlying hematological disorder (8). It should be noted that RTX has shown clinical and immunological efficacy in all patients, however with a high rate (50 %) of clinical relapses (mean 13.5 months). Tolerance was marked by the occurrence of side-effects (50 %), including severe infections in 6 patients, which occurred in a particular subset of patients: age older than 70 years, with renal failure and high-dose corticosteroids. The authors concluded that RTX showed a dramatic efficacy and a steroid-sparing effect, although safety concerns remained a strong consideration.

The second study come from the largest French CryoVas survey including patients (*n*=242) with non-viral CryoVas, in order to evaluate safety and efficacy of different therapeutic regimens. The analysis showed that RTX plus corticosteroids had the greater therapeutic efficacy compared with corticosteroids alone, as well as with cyclophosphamide plus corticosteroids. However, the approach including RTX was associated with high rates of severe infections (HR 1.7, *p*=0.41), especially with high doses of corticosteroids [14••]. However, no significant differences in death rates were found in this study.

In conclusion, the available evidence suggests that RTX is the most effective therapy in non-viral CryoVas; however, its safety profile should be considered.

Type I CryoVas

Management of type I CryoVas patients should be individualized based on severity of clinical manifestations and the underlying hematological disorder. Regimens including bortezomib, lenalidomide, thalidomide, and RTX have been investigated in Type I CryoVas. In patients with multiple myeloma, some investigators have suggested initiation of plasmapheresis or plasma exchange along with therapy for underlying hematological disorder [20]. However, as type I CryoVas related to MGUS is more severe, therapy should include different approaches, ranging from corticosteroids

and cyclophosphamide, to new biologic agents such as bortezomib, lenalidomide, and RTX.

The efficacy of RTX in Type I CryoVas is still under debate [21, 22]. In the largest series of Type I CryoVas, data from 22 patients on RTX therapy have shown an efficacy rate of 80 % in first- or second-line treatment, supporting its use in naive or relapsing/refractory patients. However, vasculitic flares were shown in 13 %, within 48 h following RTX infusion. RTX should be administered with caution in elderly patients with renal failure receiving high-dose corticosteroids due to the increased risk of severe infections. Data regarding the safety and efficacy of alternative regimens, including thalidomide, lenalidomide, and bortezomib, have also been reported. The efficacy rate of thalidomide and lenalidomide was shown to be nearly 80 % [23, 24], while a bortezomib-based regimen was shown to be effective in 86 %. All of them were well tolerated. Overall, these findings suggest that patients with severe/refractory type I CryoVas, RTX-thalidomide, lenalidomide, and bortezomib regimens could be interesting and appropriate alternative options when combined with corticosteroids.

Conclusions

Although more than 80 % of CryoVas are associated with HCV infection, clinicians should be aware of non-infectious causes of CryoVas. Non-infectious mixed CryoVas seems to have a similar disease expression and outcomes as compared to HCV-related CryoVas. In addition, patients with type I CryoVas showed a higher frequency of severe cutaneous lesions and high levels of serum cryoglobulins. Careful individual work-up to assess the severity of involvement is important when planning therapeutic approaches. Regarding new biologic agents, RTX showed to be dramatically effective but remains associated with severe infections in a subset of patients. The treatment of type I CryoVas is primarily that of the underlying hematological malignancy using the optimal combined chemotherapy. In this setting, the use of RTX, thalidomide-, lenalidomide-, and bortezomib-based regimens has shown to be effective, although their use deserves further investigation.

Compliance with Ethics Guidelines

Conflict of Interest Luis R. Espinoza declare that he has no conflict of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

- 1.• Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. *Curr Opin Rheumatol*. 2013;25:10–8. *Comprehensive report with a complete literature review on clinical and laboratory manifestations and new therapeutic approaches of cryoglobulinemia vasculitis.*
2. Lerner AB, Watson CJ. Studies of cryoglobulins I: unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). *Am J Med Sci*. 1947;214:410–5.
3. Brouet JC, Clauvel JP, Danon F, et al. Biologic and clinical significance of cryoglobulins: a report of 86 cases. *Am J Med*. 1974;57:775–88.
4. Trejo O, Ramos-Casals M, Garcia-Carrasco M, et al. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine (Baltimore)*. 2001;80:252–62.
5. Saadoun D, Sellam J, Ghillani-Dalbin P, et al. Increased risks of lymphoma and death among patients with nonhepatitis C virus-related mixed cryoglobulinemia. *Arch Intern Med*. 2006;166:2101–8.
- 6.•• Ramos-Casals M, Stone JH, Cid MC, et al. The cryoglobulinaemias. *Lancet*. 2012;379:348–60. *An outstanding review with a complete description of pathophysiology, clinical manifestations, diagnosis, and treatment approaches of cryoglobulinemia vasculitis.*
7. Della Rossa A, Tavoni A, Bombardieri S. Hyperviscosity syndrome in cryoglobulinaemia: clinical aspects and therapeutic considerations. *Semin Thromb Hemost*. 2003;29:473–7.
8. Gorevic PD, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am J Med*. 1980;69:287–308.
9. Tzioufas A, Boumba D, Skopouli F, et al. Mixed monoclonal cryoglobulinaemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjogren's syndrome. *Arthritis Rheum*. 1996;39:767–72.
10. Brito-Zerón P, Ramos-Casals M, Bove A, et al. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. *Rheumatology (Oxford)*. 2007;46:1359–62.
11. García-Carrasco M, Ramos-Casals M, Cervera R, et al. Cryoglobulinaemia in systemic lupus erythematosus: prevalence and clinical characteristics in a series of 122 patients. *Semin Arthritis Rheum*. 2001;30:366–73.
12. Morra E. Cryoglobulinemia. *ASH Education Book. Hematol Am Soc Hematol Educ Program*. 2005;1:368–72.
13. Trejo O, Ramos-Casals M, López-Guillermo A, et al. Hematologic malignancies in patients with cryoglobulinaemia: association with autoimmune and chronic viral diseases. *Semin Arthritis Rheum*. 2003;33:19–28.
- 14.•• Terrier B, Krastinova E, Marie I, et al. Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. *Blood*. 2012;119:5996–6004. *This is the largest series so far published on non-infectious mixed CryoVas analyzing the safety and efficacy of different treatment approaches. Rituximab and corticosteroids showed greater efficacy although were associated with severe infections.*
15. Damoiseaux J and Cohen Tervaert JW. Diagnostics and treatment of cryoglobulinemia: it takes two to tango. *Clin Rev Allerg Immunol* 2013.
- 16.•• Terrier B, Karras A, Kahn J, et al. The spectrum of type I cryoglobulinemia vasculitis. *Medicine*. 2013;92:61–8. *This study describes the presentation, prognosis, and therapeutic management of the largest series of type I CryoVas patients. Severe cutaneous manifestations and high serum cryoglobulin levels characterized type I CryoVas, although the frequency of glomerulonephritis was lower than expected.*
- 17.• Terrier B, Carrat F, Krastinova E, et al. Prognostic factors of survival in patients with non-infectious mixed cryoglobulinaemia vasculitis: data from 242 cases included in the CryoVas survey. *Ann Rheum Dis*. 2013;72:374–80. *This study included 242 patients with non-infectious mixed CryoVas. Causes of death and prognostic factors of survival were assessed and a prognostic score was determined to predict survival at 5 years. Main prognostic factors were age older than 65 years, pulmonary and gastrointestinal involvement, and renal failure.*
18. Terrier B, Semoun O, Saadoun D, et al. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. *Arthritis Rheum*. 2011;63:1748–57.
19. Terrier B, Launay D, Kaplanski G, et al. Safety and efficacy of rituximab in nonviral cryoglobulinemia vasculitis: data from the French Autoimmunity and Rituximab registry. *Arthritis Care Res (Hoboken)*. 2010;62:1787–95.
20. Payet J, Livartowski J, Kavian N, et al. Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. *Leuk Lymphoma*. 2013;54(4):767–77.
21. Nehme-Schuster H, Korganow A, Pasquali J, et al. Rituximab inefficiency during type I cryoglobulinemia. *Rheumatology (Oxford)*. 2005;44:410–1.
22. Pandrangi S, Singh A, Wheeler D, et al. Rituximab treatment for a patient with type I cryoglobulinemic glomerulonephritis. *Nat Clin Pract Nephrol*. 2008;4:393–7.
23. Calabrese C, Faiman B, Martin D, et al. Type 1 cryoglobulinemia: response to thalidomide and lenalidomide. *J Clin Rheumatol*. 2011;17:145–7.
24. Lin R, Curran J, Zimmerman T, et al. Lenalidomide for the treatment of cryoglobulinemia and undifferentiated spondyloarthritis in a patient with multiple myeloma. *J Clin Rheumatol*. 2010;16:90–1.