

Alveolar hemorrhage in cryoglobulinemia – an indicator of poor prognosis

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Abstract

Objective

Alveolar vasculitis is an unusual event in the course of cryoglobulinemia (CG). The inflammatory process involving the alveolar capillary walls may result in severe alveolar hemorrhage and consequently lead to a grave outcome. The objective of this study was to evaluate the occurrence of this unusual finding in CG.

Methods

We reviewed the records of all patients with CG who developed acute alveolitis, registered their associated clinical and laboratory parameters and evaluated the possible impact these parameters may have on their prognosis. In addition we scanned the Medline for similar cases.

Results

Of the 125 patients with CG who were hospitalized in our medical center during the last 23 years, 4 (3.2%) developed alveolar hemorrhage. All patients exhibited extreme fatigue, fever with clinical and radiological evidence of alveolitis. Of the 4 new cases, 1 had type II CG and 3 had type III CG. Of our 4 patients, 3 developed concomitant acute renal failure necessitating hemodialysis. A literature survey resulted in 6 additional cases. All 10 patients experienced acute respiratory insufficiency and eight had at least one episode of hemoptysis. In the other 2 patients the bronchoalveolar lavage (BAL) fluid contained hemosiderin laden macrophages. Five of the 10 patients had concomitant hepatitis C virus (HCV) infection; 2 patients were seen prior to modern identification of the HCV; however, liver abnormalities were not described. Of the 10 patients 5 patients had type II CG and 5 others had type III. Of the 7 patients in whom outcome was available, 6 died from their illness. Acute renal failure or exacerbation of antecedent glomerular disease occurred in 8 patients.

Conclusions

Alveolitis is a rare manifestation of CG, presenting as an overwhelming systemic illness and portends a poor prognosis with a high mortality rate.

Key words

Hemoptysis, cryoglobulinemia, hepatitis C infection, Hodgkin's lymphoma, respiratory insufficiency, acute renal failure.

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Introduction

Cryoglobulins are serum immunoglobulins that precipitate on exposure to cold temperature, and redissolve with re-warming. CG is associated with wide a clinical spectrum including systemic features as fever, malaise, purpura, arthralgia, polyneuropathy and renal involvement (1).

The chemical characteristics of the cryoglobulins categorize the clinical expression of the disorder. Type I CG is associated with hematological malignancies and the cryoglobulins are usually a monoclonal paraprotein. Type II CG is frequently associated with chronic HCV infection and the cryoglobulin fraction is comprised of both polyclonal IgG and a monoclonal IgM rheumatoid factor directed against the IgG. Patients with type III have mixed cryoglobulin isotypes that are polyclonal and carry rheumatoid factor activity. This type coexists with chronic infections as HCV that occurs in about half of the patients as well as with chronic inflammatory, autoimmune and lymphoproliferative conditions (2-4).

A recent study of Ferri *et al.* (5) encompassed 231 patients with CG. Mild exertional dyspnea occurred in 26% of them. Clinically evident interstitial lung involvement was observed in only 4 (2% of the cases) of them. One of these patients developed a severe episode of hemoptysis.

In this communication we describe four patients who developed a diffuse alveolar hemorrhage, often with a co-existent glomerulonephritis that resulted in a grave outcome.

Patients and methods

We retrospectively studied the epidemiological, clinical and immunological characteristics of 4 (3.2%) out of 125 patients with CG who were hospitalized at the Hadassah Medical Center Jerusalem Israel, between the years 1980-2003 due to acute alveolitis and investigated the contribution of the pulmonary vasculitis and hemorrhage to the outcome of their disease. The clinical presentations of the four new cases are described in brief. Additionally, the English medical literature was scanned by using the *Pubmed* medline service

for similar previous cases and a complete analysis of all cases was performed.

Patient no. 1

A fifty year-old male patient with chronic HCV infection for more than a decade was admitted due to respiratory and renal insufficiency. During the previous three years he was diagnosed with type III mixed CG (with no paraprotein) with a positive rheumatoid factor (RF) and a cryocrit of 4%. Despite interferon treatment for several months he developed a purpuric rash, left hemiparesis with cerebellar signs, and concomitant deterioration of kidney functions; an active sediment and massive proteinuria were also recorded. A kidney biopsy demonstrated membranoproliferative lesions and a stereotactic cerebellar brain biopsy disclosed vasculitic lesions. He developed progressive respiratory insufficiency and was given oxygen supplementation. Patchy lung infiltrates were detected on the chest radiograph. A BAL demonstrated multiple macrophages filled with hemosiderin. Following pulse methylprednisolone therapy his condition stabilized. The patient convalesced following several cycles of plasmapheresis but his disease relapsed two years later with respiratory and renal deterioration. No evidence for pulmonary hemorrhage was observed on bronchoscopy but giant cells and a positive PCR test for cytomegalovirus were detected. Resumption of the previous therapeutic regimen was unsuccessful and despite the addition of ganciclovir he died.

Patient no. 2

A 41-year-old male with known HCV infection with concomitant type III mixed CG and membranoproliferative glomerulonephritis was hospitalized due to respiratory distress and renal deterioration. For many years he had received azathioprine or cyclophosphamide for his renal disease. Despite continuous presence of viral RNA and CG he was not given interferon therapy. Four months prior to the patients' final hospitalization he developed subfebrile fever accompanied by severe malaise, thrombocytopenia, anemia and a purpuric cutaneous eruption that was found

to be leukocytoclastic vasculitis on biopsy. On admission he had a cryocit of 7%. After several days he developed acute respiratory and renal insufficiency that necessitated oxygen supplementation and hemodialysis. Methylprednisolone pulse and cyclophosphamide were added. Several newly formed infiltrates were detected on a chest radiograph that did not resolve following administration of antibiotics. A BAL demonstrated many hemosiderin laden macrophages. His condition stabilized temporarily. In an attempt to preserve and consolidate this short-lived clinical remission treatment with Rituximab (anti-CD20 antibodies) was initiated. Unfortunately, he expired several weeks later from septic shock.

Patient no. 3

Seven years prior to his final hospitalization, a 48-year-old man received a blood transfusion while undergoing a resection of a cervical neurinoma, and was later found to have chronic HCV infection. Attempts to treat him with interferon and ribavirin ended prematurely due to the development of leucopenia, thrombocytopenia and elevated serum thyroid-stimulating hormone levels. During the year prior to this admission the appearance of a RF in his serum was noticed followed by continuous malaise, relapsing high fevers, and persistent flu-like symptoms. Subsequently, he developed a continuous cough that partially subsided following azithromycin therapy. The abrupt appearance of respiratory and renal insufficiency, hemoptysis, an increasing degree of malaise, fever, diffuse purpura and extreme myalgia prompted referral to our service. Cryoglobulinemia with a positive RF and a 4% cryocit was detected but no paraprotein. Therapy with six cycles of plasmapheresis, pulse therapy with methylprednisolone combined with cyclophosphamide and hemodialysis induced a brief remission and normalization of kidney function. However, he developed CMV pneumonia and responded promptly to ganciclovir therapy. Several weeks later he was readmitted with similar clinical picture and recurrent hemoptysis. A bronchoscopy exhibited a frail edema-

tous mucosa but no giant cells were revealed in the histopathology neither was a PCR test for CMV. Despite aggressive therapy he succumbed to progressive respiratory failure.

Patient no. 4

A forty-year old woman was diagnosed with stage IIa Hodgkin's lymphoma. She was treated with the administration of six cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), however afterwards cryoglobulins (cryocit – 15%), an IgG paraprotein and RF and antinuclear antibody activity were detected with no markers of HCV infection. A year following completion of chemotherapy she was readmitted due to progressive malaise, fever, a purpuric cutaneous eruption, gastrointestinal bleeding, a single episode of hemoptysis and a mild thrombocytopenia. Over several days her respiratory condition deteriorated sharply and did not improve despite antibiotic therapy. A BAL was performed that demonstrated hemosiderin filled macrophages but no evidence of an infectious agent. A chest radiograph was compatible with severe diffuse pulmonary vasculitis. Despite intravenous pulse therapy with methylprednisolone combined with cyclophosphamide and six sessions of plasmapheresis she succumbed to respiratory failure due to the pulmonary involvement.

Discussion

Although subtle pulmonary involvement is a common finding among patients with CG, comprehensive studies dealing with this issue have not been performed. By and large the respiratory symptoms do not draw much attention and they tend to occur more often among patients with the mixed types of CG than in the type I of CG (6,7). Bombardieri *et al.* (8) observed roentgenographic evidence of interstitial lung disease in 18 patients of 23 with CG. Interestingly, 20 of these patients (87%) had absent or only moderate symptoms. Spirometric tests were indicative of small airway disease and impairment of gas diffusion but only 4 were symptomatic.

Bronchiolitis obliterans organizing pneumonia, pulmonary vasculitis and pulmonary hemorrhage are more severe presentations but occur scarcely (5-7). In a large series Ferri *et al.* (5) reported that clinically evident interstitial pulmonary disease was an unusual manifestation appearing in 4 of 210 patients. Only one developed hemoptysis, a finding corroborated by this and other reports (9). In the current study we found a lower rate of 3.2% (4 of 125 patients with CG) who presented with alveolar hemorrhage.

In addition to the 4 patients we describe in this communication 6 previous reports of CG patients with severe alveolar hemorrhage have been published over the last thirty years (9-13). Two of the 10 patients were female and 8 were male. Five patients had type II CG and the other 5 had type III CG. No outcome difference was noted between these two groups (Table I).

Data supporting the evidence of either antecedent or concurrent renal disease existed in 9 of the 10 patients. In almost all of the patients with renal involvement acute renal failure appeared concurrently with diffuse alveolar hemorrhage. Five patients had associated HCV infection and one had concomitant Hodgkin's lymphoma. Two of the patients were described prior to the advent of modern identification methods of HCV.

The presentation in these patients was acute and severe. The available data indicate that the alveolar hemorrhage was a direct cause of death in six of them. It is clear that renal involvement also contributed to the ominous outcome; glomerulonephritis with renal failure is the leading cause of death in CG, occurring in a third of mixed CG patients. However, two primary concomitant clinical manifestations in a single patient such as those we reported are uncommon. Ferri *et al.* (5) described only 2 cases in whom the involvement of two major systems were the direct cause of death during a follow-up period of 79 of 97 deceased patients in whom the cause of death was ascertained.

BAL may have an important contribution to the diagnosis of lung involve-

Table 1. Clinical data of all patients with cryoglobulinemia with alveolar hemorrhage described in the English medical literature.

No/ gender	Type of CG	Cryocrit (%) cryoglobulin composition, C ₃ , C ₄ concentra- tions (mg/dl) and other autoantibodies	Duration of CG prior to alveolitis (yrs.)	Age at onset of alveolitis (yrs.)	Concomitant medical condition	Duration of hepatitis (yrs.)	Other illnesses	Manifestations concomitant with alveolitis	Therapy	Outcome	Reference
Patient 1/M	3	Cryocrit - 4% C3, - 71 C4, - 29 RF+	3	50	HCV Viral load >10 ⁵ RNA/ml	13	MPGN, Diabetes mellitus type 2	Generalized weakness, fever, alveolitis, cutaneous lesions, anemia, thrombocytopenia, gastrointestinal bleeding, a cute renal failure	Methyl/prednisolone, cyclophosphamide, plasmapheresis, hemodialysis	Death 2 years following therapy due to a similar crisis	Current communication
Patient 2/M	3	Cryocrit - 7% C3, - 67 C4, - 25 RF+	8	41	HCV Viral load >10 ⁵ RNA/ml	23	MPGN	Generalized weakness, fever, alveolitis, cutaneous lesions, anemia, thrombocytopenia, acute renal failure	Methyl/prednisolone, cyclophosphamide, plasmapheresis, anti-CD20 (Rituximab), hemodialysis	Death during hospitalization (septic shock)	Current communication
Patient 3/M	3	Cryocrit - 4% C3, - 16 C4, - 0 RF+	Recent diagnosis	48	HCV	22		Generalized weakness, fever, alveolitis with hemoptysis, cutaneous lesions, anemia, thrombocytopenia, acute renal failure	Methyl/prednisolone, cyclophosphamide, plasmapheresis, hemodialysis	Death during hospitalization	Current communication
Patient 4/F	2	Cryocrit - 15% C3, - 33 C4, - 0 RF+ IgG paraprotein	1	40	Hodgkin's lymphoma (stage IIa)			Generalized weakness, fever, alveolitis with hemoptysis, cutaneous lesions, anemia, thrombocytopenia, gastrointestinal bleeding	Methyl/prednisolone, cyclophosphamide, plasmapheresis	Death during hospitalization	Current communication
Patient 5/M	3	RF+, cryocrit - 11% Cryoglobulins IgG, IgM	3	54			MPGN	Dyspnea, hemoptysis, Raynaud's phenomenon, mild renal failure	Methyl/prednisolone	Recovery	8
Patient 6/M	2	RF+, cryocrit - 4.4% Cryoglobulins IgG, paraprotein IgM, poly IgG, IgA		61				Dyspnea, hemoptysis, Raynaud's phenomenon, renal failure, leg ulcers, gangrene, joint disease, neuropathy	Plasmapheresis	Recovery	9
Patient 7/M	2	paraprotein IgM poly IgG	4	49			GN	Hemoptysis, dyspnea, renal, failure, hypertension, fever	Corticosteroids and immunosuppressive therapy		10
Patient 8/F	2	RF+, cryocrit - 13% paraprotein IgM, poly IgG	Recent diagnosis	48	HCV	6	MPGN	Hemoptysis, dyspnea, purpura, renal failure	Methyl/prednisolone, cyclophosphamide, azathioprine, plasmapheresis, interferon α	Death due to septic shock	11
Patient 9/W	2				HCV		GN	Hemoptysis, asthma, dyspnea purpura, renal failure, purpura	Methyl/prednisolone		12
Patient 10/M	3	+ 4 cryoprecipitate RF+	36				Mental retardation, subacute proliferative glomerulo- nephritis	Malaise, nausea, fever, hypertension, pitting edema, Raynaud's syndrome, nephrotic syndrome, hemoptysis, dyspnea, acute renal failure	Methyl/prednisolone, heparin, peritoneal dialysis	Death due to respiratory insufficiency	13

M: male; F: female; HCV: hepatitis C virus; MPGN: membranoproliferative glomerulonephritis; CG: cryoglobulinemia; ANA: antinuclear antibodies; RF: rheumatoid factor; c.p ANCA: c.p antineutrophil cytoplasmic antibodies; GBM: anti-glomerular basement membrane antibodies.

ment in CG. Manganelli *et al.* (14) found a lower percentage of alveolar macrophages and a higher percentage of lymphocytes comparing BAL findings of non-smoking female patients with mixed CG free of respiratory symptoms to healthy controls. Additionally the percentage of CD3+ lymphocytes was higher in the CG patients; their findings suggest that BAL results may mark a subclinical T-lymphocytic alveolitis in CG prior to the deterioration in pulmonary function. BAL also has a major role identifying pathogenic agents that may aggravate respiratory functions. Early BAL is essential whenever clinical suspicion of pulmonary CG is raised in order to decide whether immunosuppressive therapy or antibiotics should be added.

Widespread vasculitis involving small- to medium-sized arteries, capillaries, and venules involving the kidneys and lungs elucidates this clinical presentation. The association of alveolitis with mixed CG rather than Type I CG suggests that immune-complexes play a major role in its pathogenesis. The immunosuppressive therapy that these patients were treated with paradoxically may lead to a more intense viral proliferation within B cells, which consequently may enhance the production of more rheumatoid factor cryoglobulins and a larger amount of giant immune-complexes containing HCV particles, anti-HCV IgG bound to a RF. Such a process may induce a fiercer immune response directed toward the alveolar surface (15).

No specific therapeutic regimen was found to be advantageous. One patient remitted following plasmapheresis therapy, but this modality was not found to be beneficial in the other cases (9). Three patients had a temporary remis-

sion following combination therapy with methylprednisolone pulse therapy, cyclophosphamide and plasmapheresis but expired following a recurrent attack, one of them occurring three years later (10). It is noteworthy that four patients developed an infection that was associated with a rapid clinical deterioration, however it is difficult to determine whether this was a result of the immunosuppressive therapy or whether the infection was the inducer of the upsurge of the CG. Two patients developed CMV pneumonia that conceivably transformed the lung parenchyma more vulnerable to subsequent immune mediated injury occurring afterwards. Recent use of Rituximab, the chimeric monoclonal anti-CD20 antibody, in non-pulmonary CG has been reported with equivocal success (16, 17). One patient in this series was treated unsuccessfully with this agent.

In conclusion, we have shown that the occurrence of alveolar hemorrhage in patients with CG also carries an inexorable course that is frequently marked by a concurrent exacerbation of renal disease and almost exclusively ends as a terminal event.

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