Case Report

Goodpasture-like Syndrome Induced by D-Penicillamine in a Patient with Systemic Sclerosis: Report and Review of the Literature

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ABSTRACT. We report a case of Goodpasture-like syndrome developing in a patient who was treated with D-penicillamine for the diffuse form of systemic sclerosis. This unusual pulmonary-renal syndrome has been described on rare occasions in patients receiving D-penicillamine. This complication appeared to be uniformly fatal unless treated with aggressive immunotherapy. We review the cases reported to date in the literature and describe the clinical characteristics, therapy, and outcome of this group of patients. (J Rheumatol 2003;30:1616–20)

Key Indexing Terms:
SYSTEMIC SCLEROSIS D-PENICILLAMINE GOODPASTURE SYNDROME
CRESCENTIC GLOMERULONEPHRITIS PULMONARY HEMORRHAGE

D-penicillamine (D-Pen), which has been used in the treatment of Wilson's disease, cystinuria, rheumatoid arthritis, primary biliary cirrhosis, lead poisoning, and systemic sclerosis (SSc), has been associated with a variety of autoimmune phenomena ranging from the production of autoantibodies to clinical presentation of autoimmune disorders including systemic lupus erythematosus (SLE), autoimmune thyroiditis, myasthenia gravis, pemphigus vulgaris, Guillain-Barré syndrome, and polymyositis[1-3]. Renal disease related to D-Pen therapy has also been described, and it usually presents with proteinuria and occasionally a nephrotic syndrome[4,5]. D-Pen induced nephrotic syndrome is usually self-limited and improves following discontinuation of the drug. Another type of renal involvement related to D-Pen therapy has been described in patients who develop symptoms and serological abnormalities of an SLE-like syndrome (Table 1). This process also usually resolves with discontinuation of the drug and only rarely is corticosteroid administration required. Rapidly progressive glomerulonephritis (RPGN) has also been reported during D-Pen therapy. In these cases severe acute renal failure and histopathologic evidence of glomerulitis with crescent formation are observed. In addition, several cases of a Goodpasture-like syndrome with RPGN and pulmonary hemorrhage have been reported[6-16]. We describe a patient who developed Goodpasture-like syndrome 30 months after initiation of D-Pen therapy for treatment of diffuse SSc. To our knowledge, this is the second reported case of this syndrome in a patient with SSc who was treated with D-Pen.

CASE REPORT

A 68-year-old Caucasian man had presented 3 years earlier with an 8 year history of Raynaud's phenomenon and ischemic digital ulcers that necessitated surgical debridement and antibiotic therapy. On presentation, he described a 6 month history of swelling, stiffness and pruritus of feet and hands, mild shortness of breath at rest with dyspnea on exertion, and palpitations. He denied having symptoms of gastroesophageal reflux or distal dysphagia. His history disclosed heavy tobacco use, an episode of atrial flutter, and iron deficiency anemia. On examination, skin sclerotic changes involving the face, hands, forearms, arms, lower legs, and anterior chest were found. Prominent telangiectasias were present on the face, lips, and hard palate. There was calcinosis on the extensor surfaces of both elbows. Dry rales were heard on auscultation of the lower lung fields. Ancillary studies revealed a moderately dilated esophagus with decreased lower esophageal sphincter pressure, bibasilar interstitial lung fibrosis, abnormal pulmonary function studies with a mild restrictive pattern, a forced vital capacity (FVC) of 72% and a marked decrease of the diffusing lung capacity (DLCO) at 19% of the predicted value. An echocardiogram was also performed showing bi-atrial enlargement, annular calcification of the mitral valve, normal left ventricular size, and normal pulmonary artery pressure. Laboratory studies revealed creatinine 1.1 mg/dl, hemoglobin 12.8 g/dl, platelet count of 235,000, creatinine phosphokinase of 47 U/l (< 235 U/l), a C3 of 75 mg/dl (50–120 mg/dl), and C4 of 20 mg/dl (15–45 mg/dl). Serologic analysis revealed antinuclear antibodies (ANA) at a titer of 1:1280 with a homogeneous pattern, a positive anti-Scl-70 antibody, a negative anticentromere antibody, and negative anti-dsDNA antibody. He was treated with D-Pen, which was slowly increased from an initial dose of 250 mg/day to a maximal dose of 1000 mg/day about one year later. Two and a half years after initiation of this therapy, he had a remarkable improvement of the skin sclerotic changes, which became limited to the

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Table 1. D-penicillamine related renal pathology.

Clinical Features	Renal Pathology	Comments
Isolated proteinuria or nephrotic syndrome	Membranous glomerulopathy, rarely minimal disease or mesangioproliferative GN	Up to 20% of patients; minimal impairment of renal function, slow resolution on discontinuation of D-Pen
SLE syndrome	Diffuse proliferative CGN with vasculitis at times	Resolution on discontinuation of D-pen; in severe cases steroids may be required
Vasculitis	Necrotizing vasculitis with minimal change or CGN	Rare; in severe cases steroids may be required
Goodpasture-like syndrome	CGN with nonlinear staining of GBM	Rapidly progressive renal/pulmonary syndrome; plasmapheresis or immunosuppression required; anti-GBM antibodies not commonly seen

CGN: crescentic glomerulonephritis; GBM: glomerular basement membrane.

digits and face. The DLCO had improved to 30% of predicted, while FVC remained at 66% of predicted.

He presented to the emergency room with sudden onset of palpitations, and rapid atrial fibrillation at 126 beats per minute was found. On presentation his blood pressure was 132/84 and his respiratory rate was 20 per minute. A funduscopic examination was unremarkable. Serum creatinine was 2.1 mg/dl and urinalysis showed 2+ protein, red cell casts, an abnormal sediment with 50–100 red blood cells and 20–50 white blood cells per high power field. His hemoglobin was 12.4 mg/dl, platelet count was 260,000, and on his peripheral smear there were no signs of hemolysis. A chest radiograph revealed bibasilar interstitial fibrosis with right lung discoid atelectasis. After admission, a myocardial infarction was excluded and he was treated with ß-blockers, anticoagulants, and antianginal medications; severe hemoptysis ensued shortly afterward. Anticoagulant therapy was discontinued. A ventilation-perfusion scan yielded a low probability of pulmonary embolus. Renal insufficiency and hemoptysis worsened and chest radiographs showed increasing alveolar infiltrates, suggestive of continued pulmonary hemorrhage (Figure 1). A presumptive diagnosis of Goodpasture-like syndrome related to D-Pen therapy was entertained and the drug was discontinued. Plasmapheresis was initiated. Serologic studies for anti-glomerular basement membrane antibodies (GBM) were negative, as were studies for anti-dsDNA. Studies for ANCAor anti-histone were not performed. Nine days after hospitalization, there was sudden deterioration and a new loud systolic murmur was detected. Echocardiography and Doppler ultrasound examination disclosed a new ventricular septal defect. He deteriorated and despite an aortic balloon pump, mechanical ventilation, and plasmapheresis, he died on the 36th day of hospitalization.

A postmortem examination revealed diffuse bilateral lung interstitial fibrosis, pulmonary artery plexiform lesions suggestive of pulmonary hypertension, and severe pulmonary hemorrhage in the right upper and middle left lower lobes of both lungs. On microscopic examination a pattern of cystic transformation of the lung parenchyma was seen in the lower lobes, as well as frequent metaplasia of the alveolar lining. The alveolocapillary membrane was replaced by interstitial fibrosis diffusely distributed throughout the lung, and profound intraalveolar hemorrhage was present (Figure 2). The kidneys showed focal segmental changes, with

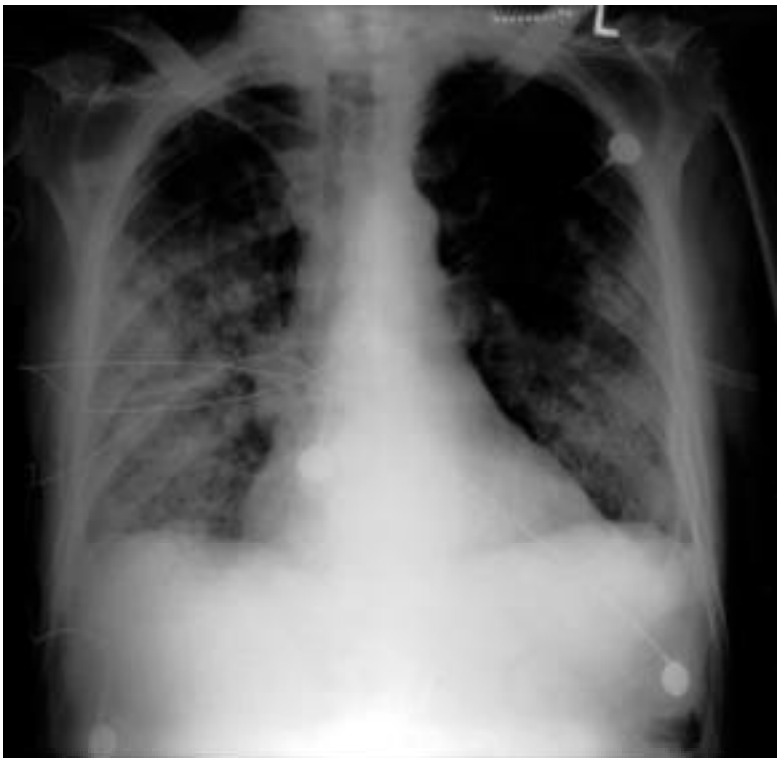

Figure 1. Chest radiograph 7 days after hospitalization, showing bibasilar and mid-lung alveolar infiltrates superimposed on basilar fibrosis.

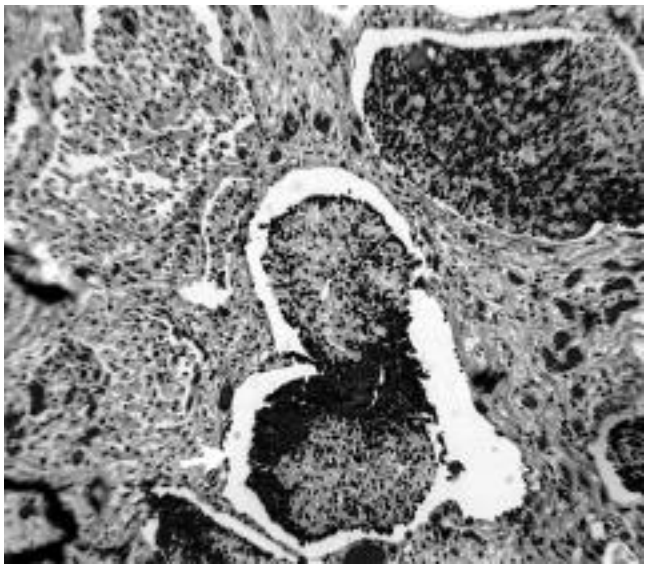

Figure 2. Postmortem lung section with replacement of the alveolocapillary membrane with interstitial fibrosis as well as severe intraalveolar hemorrhage (arrow).

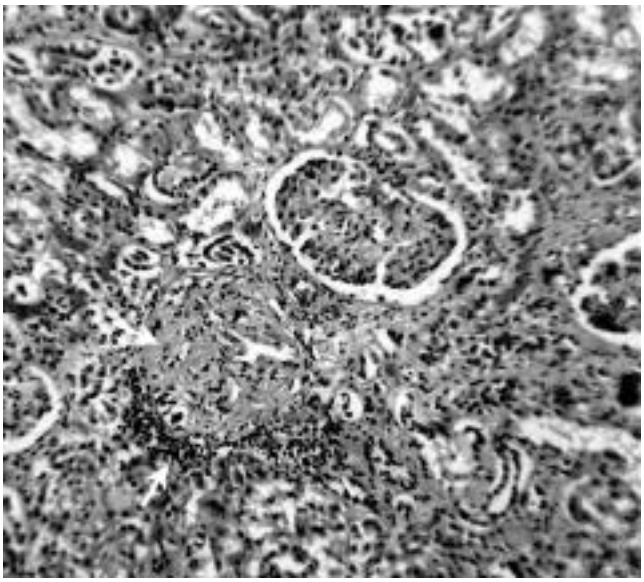

Figure 4. Postmortem kidney section with crescent formation (top arrow) and adjoining inflammatory infiltrate (bottom arrow).

sclerotic crescents in some glomeruli. In some glomeruli the segmented changes were moderately proliferative, but the overall appearance was of a focal, segmental sclerosing glomerulopathy. In some sections periglomerular inflammatory infiltrates were present (Figures 3 and 4). No evidence of necrosis, fibrin deposition, arteritis, microangiopathy, or intravascular thrombi was seen. There was mesangial thickening due to an increase in the mesangial matrix seen on periodic acid-Schiff stain. Immunofluorescence studies showed diffuse, global granular deposits in the glomeruli, with no staining for IgG, IgM, IgA, or C3 deposits. Electron microscopy revealed diffuse thickening of the glomerular basement membrane. Cardiac examination showed severe coronary artery disease, a recent anterior wall infarct with a fresh extension, and rupture of the ventricular septum.

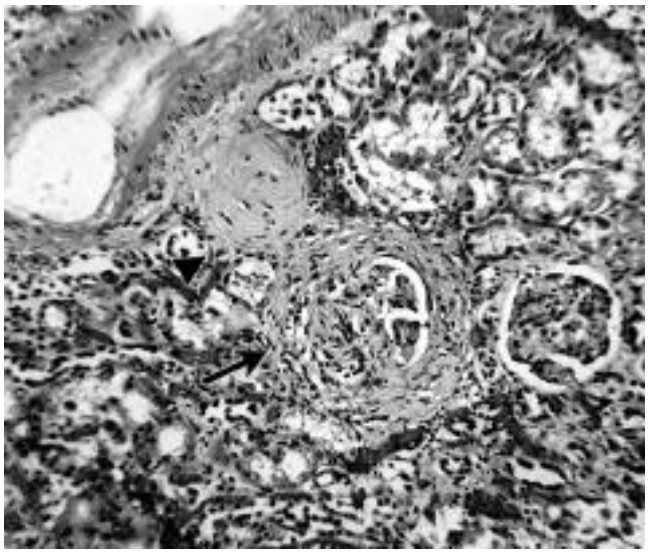

Figure 3. Postmortem kidney section with crescent formation (arrow) and adjoining sclerosed glomerulus (arrowhead).

DISCUSSION

D-penicillamine therapy has been shown to induce a wide range of autoimmune diseases in animal models and, of relevance to the patient described here, glomerulonephritis associated with anti-GBM antibodies[17]. Renal pathology secondary to D-Pen treatment for SSc should be differentiated from renal involvement related to the underlying SSc. The typical presentation of SSc renal involvement is SSc renal crisis, a fulminant form of oliguric renal failure with severe hypertension, hemolytic microangiopathic changes, and rapidly progressive renal failure. Histopathological examination in these cases, however, does not show any evidence of glomerulitis. Another presentation of renal involvement in SSc is that of isolated proteinuria, which may be difficult to differentiate from proteinuria or nephrotic syndrome secondary to D-Pen. The most common renal involvement caused by D-Pen therapy is isolated proteinuria, or in severe cases nephrotic syndrome (Table 1). In these patients, membranous and mesangial changes are the predominant histopathologic abnormalities. The proteinuria and the nephrotic syndrome are usually self-limited and improve without treatment once D-Pen is withdrawn. Another renal lesion, reported on rare occasions in patients receiving D-Pen, is a necrotizing vasculitis, which can usually be adequately treated with corticosteroids[18]. In patients receiving D-Pen who develop an SLE-like syndrome, renal involvement may also be present. In these cases, a diffuse proliferative glomerulonephritis is observed in kidney biopsy specimens. This form of renal involvement is also self-limited once the medication is withdrawn, and it requires use of corticosteroids only rarely[18].

A Goodpasture-like syndrome with typical crescentic

glomerulonephritis has also been described[6-16]. However, these cases lack anti-GBM antibodies as illustrated here. The lack of anti-GBM antibodies in most of these cases suggests the possibility that D-Pen might sensitize the host against basement membrane epitopes that are different from those present in Goodpasture syndrome, or expose hidden epitopes that trigger the production of non-GBM antibodies, explaining the Goodpasture-like presentation with the absence of anti-GBM antibodies. A total of 14 cases of pulmonary hemorrhage and a rapidly progressive glomerulonephritis related to D-Pen have been reported. A review of these cases indicates that the average duration of D-Pen therapy before the occurrence of the initial symptoms was 37 months (range 7–84 mo) at an average maximum dose of 1.3 g/day (0.5–3.5 g/day) (Table 2) before occurrence of initial symptoms. A test for anti-GBM antibodies was positive in only one of the 14 reported cases. All patients had either diffuse interstitial infiltrates or bibasilar infiltrates on chest radiographs at presentation. Renal biopsy specimens were available in 12 patients. All revealed crescentic glomerulonephritis on histopathologic examination. Immunofluorescence was performed in 10 specimens. The results showed granular deposits of C3, IgG, or IgM or a combination of the 3 in 6 of the 10 cases. In 4 patients, including the one described here, there were no immunoglobulin or C3 deposits, and 2 of these 4 displayed granular fibrinogen deposits. Differentiation of these pathologic findings from a pauci-immune necrotizing, crescenting glomerulonephritis with an associated pulmonary-renal syndrome is difficult, although staining for linear or granular glomerular deposits favors a diagnosis of anti-GBM renal disease. The possibility of an ANCA positive glomerulonephritis with pulmonary involvement unrelated to D-Pen use should also be entertained in these patients, since this has already been reported in patients with SSc, although in our case this is less favored, since there is absence of small vessel vasculitis[19].

The development of Goodpasture syndrome in this cohort was a very serious event leading to death in 6 patients. The patients who received no pharmacologic therapy died less than 3 months from the onset of symptoms despite treatment with plasmapheresis or peritoneal dialysis. Two patients received only corticosteroids; one of them died within 6 months, whereas the second one recovered. Seven patients received corticosteroids and immunosuppressive therapy such as azathioprine and/or cyclophosphamide. Five out of these 7 patients had total recovery with resolution of the pulmonary hemorrhage and improvement of renal function; 2 had improvement of pulmonary symptoms but progressed to endstage renal disease that necessitated chronic hemodialysis (Table 3).

It can be concluded from these observations that early recognition of this severe adverse effect of D-Pen and prompt institution of a combination of immunosuppressive therapies may decrease the morbidity and mortality in these patients. Rheumatologists who prescribe D-penicillamine for the treatment of rheumatoid arthritis and SSc should be aware of this very serious and potentially fatal effect of the drug.

Table 2. Summary of clinical data of patients reported with Goodpasture-like syndrome during D-Pen therapy.

Patient	Age/sex	Diagnosis	Maximum D-Pen, g/day	Duration D-Pen, mo	Serum Creatinine, mg/dl	Chest Radiograph	Autoantibodies	Renal Histology	Renal Immuno.
1[6]	46M	Wilson's	3.5	33	8	BBI	ANA+	CGN	Gran IgG/C3
2[6]	18F	Wilson's	2	24	NR	BBI	NR	NR	NR
3[6]	30F	Wilson's	2	42	NR	DII	NR	CGN	NR
4[7]	51M	RA	1.2	32	9.5	BBI	NR	CGN	Negative
5[8]	39F	RA	1	10	NR	NR	GBM–	CGN	NR
6[9]	39F	PBC	1	25	1.2	BBI	GBM–	NR	NR
7[10]	53F	RA	0.75	84	10.8	DII	GBM–	CGN	Gran IgG/C3
8[11]	20F	RA	0.75	7	4.4	BAI	ANA+, GBM–	CGN	C3 deposits
9[12]	54F	RA	1.75	24	6	DII	NR	CGN+ necrosis	Gran IgG, M/C3
10[13]	56F	SSc	1.5	27	13.2	DII	ANA+, GBM–	CGN+ necrosis	C3 deposits
11[14]	51F	RA	0.9	84	2.4	BAI	ANA+, GBM+	CGN+ necrosis	Negative
12[15]	55F	RA	0.75	60	4	DAI	ANA–, GBM–, ANCA–	CGN	Gran fibrinogen
13[16]	22F	RA	0.5	36	6.8	BBI	ANA+, GBM–, p-ANCA+	CGN+ necrosis	Gran IgG, M/C3
Present case	68M	SSc	1	30	2.1	BBI	ANA+, GBM–, Scl-70+, ACA–	CGN	Gran fibrinogen

RA: rheumatoid arthritis, PBC: primary biliary cirrhosis, SSc: systemic sclerosis, NR: not recorded, BBI: bilateral basilar infiltrates, DII: diffuse interstitial infiltrates, BAI: bilateral alveolar infiltrates, DAI: diffuse alveolar infiltrates, ANA: antinuclear antibodies, GBM: antiglomerular basement membrane, ANCA: antineutrophil cytoplasmic antibodies, Scl-70: antitopoisomerase I antibody, ACA: anticentromere antibody, CGN: crescentic glomerulonephritis, gran: granular, PD: peritoneal dialysis.

Table 3. Therapy and outcome.

Patient	Therapy	Outcome
1	PD	Died in 3 weeks
2	PD	Died in 6 days
3	P	Died in 6 months
4	P+AZA+HD	ESRD
5	NR	Died in 3 months
6	Pla+P+AZA	Recovery
7	P+C+Pla+HD	Recovery
8	P+AZA+C+Pla	Recovery
9	NR	Died in 2 months
10	P+AZA+HD	Recovery
11	P+C+Pla+HD	Recovery
12	P	Recovery
13	P+C+Pla+HD	ESRD
Case	Pla	Died in 1 month

P: prednisone, AZA: azathioprine, HD: hemodialysis, Pla: plasmapheresis, C: cyclophosphamide, ESRD: endstage renal disease, GN: glomerulonephritis, PD: peritoneal dialysis, NR: not recorded.

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