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Glenn Tetsu Nagami
Yale University

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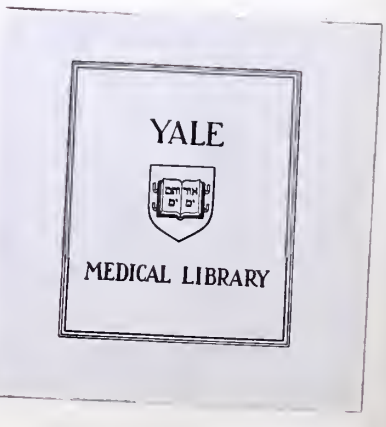

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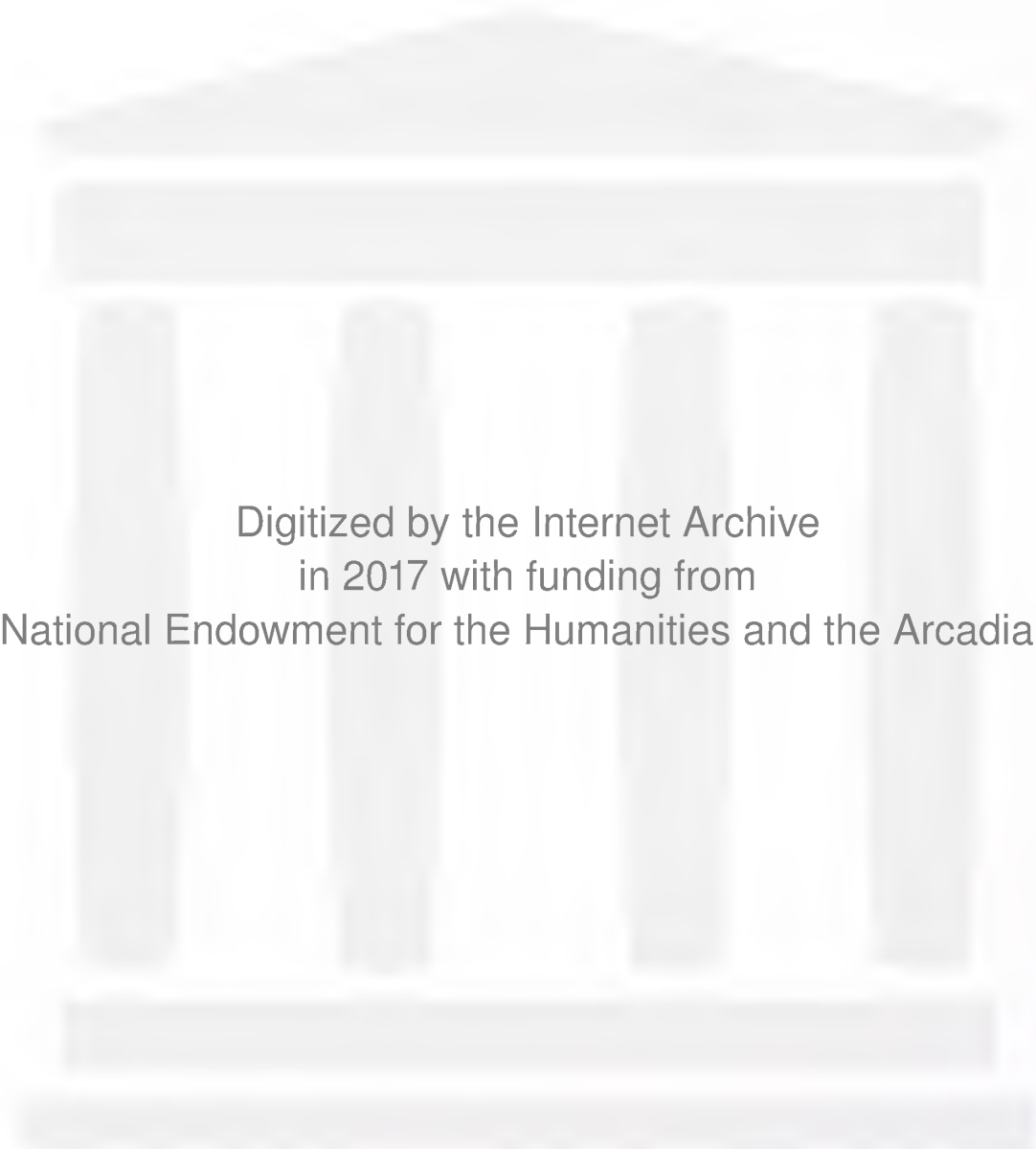

NEW INSIGHTS INTO GOODPASTURE'S SYNDROME

by

Glenn Tetsu Nagami

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To my parents....

ABSTRACT

One hundred sixty-three cases of Goodpasture's syndrome from the English literature and our files were reviewed in order to gain insight into the clinical and laboratory characteristics of this condition and the efficacy of various modes of treatment used in this syndrome. Fifty-three cases met the criteria for a definite diagnosis of Goodpasture's syndrome: 1) pulmonary hemorrhage; 2) glomerulonephritis; and 3) evidence of anti-glomerular basement membrane (anti-GBM) antibody formation. One hundred ten fulfilled the first two criteria but did not have immunologic studies documenting the presence of anti-GBM antibodies; these cases were considered to have a presumptive diagnosis of Goodpasture's syndrome.

The clinical features of patients with the definite diagnosis of Goodpasture's syndrome were similar to those of patients with the presumptive diagnosis. Young males were most frequently afflicted. Pulmonary symptoms such as hemoptysis, cough and dyspnea were prominent presenting features. Renal symptoms such as gross hematuria, edema, and flank pain occurred less frequently. Common abnormal laboratory findings included infiltrates on chest X-ray examination, anemia, hematuria, and proteinuria.

Renal function at initial hospitalization and renal biopsy specimen morphology may serve as prognostic indicators. Diminished renal function and diffuse glomerular involvement frequently presaged the onset of chronic renal failure and death. Diffuse glomerular involvement also appeared to be associated with death from fatal pulmonary hemorrhage.

Maintenance dialysis appeared to be an important factor for the improved outlook of patients with Goodpasture's syndrome. Plasmapheresis, nephrectomy,

and immunosuppressive agents seemed to have improved survival. Nevertheless, a controlled study comparing the various therapeutic modalities is needed to evaluate accurately the relative efficacy of each form of therapy.

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INTRODUCTION

Stanton and Tange (1) were the first to apply the eponym, Goodpasture's syndrome, to cases of pulmonary hemorrhage associated with glomerulonephritis. Because the pathogenic role of anti-glomerular basement membrane (anti-GBM) antibodies was not known at that time, their definition was purely clinical and, consequently, included a variety of disease entities such as uremia with congestive heart failure, glomerulonephritis with bacterial pneumonia, renal vein thrombosis with pulmonary embolism, Wegener's granulomatosis, polyarteritis nodosa, and systemic lupus erythematosis. Until the discovery of the importance of anti-glomerular basement membrane (anti-GBM) antibodies in the pathogenesis of the nephritis and lung hemorrhage (2, 3), the diagnosis of Goodpasture's syndrome could be made only after excluding the presence of clearly distinguishable conditions which could produce pulmonary hemorrhage and nephritis (4, 5). The current definition of Goodpasture's syndrome includes the triad of: 1) pulmonary hemorrhage; 2) glomerulonephritis; and 3) evidence of anti-GBM antibody formation (6, 7). This definition of Goodpasture's syndrome excludes those conditions in which pulmonary hemorrhage and glomerulonephritis may co-exist but anti-GBM antibody rarely, if ever, occurs. With this more precise definition it is possible to attempt to define more clearly the clinical spectrum of this disease. The purpose of the present study is to summarize our own experience and to review those cases reported in the literature of Goodpasture's syndrome. Special attention was directed toward the major clinical and laboratory features of the syndrome and to an analysis of the therapeutic modalities employed in this condition.

METHODS

The clinical records of all patients fulfilling the criteria of Goodpasture's syndrome at the Yale-New Haven Hospital during the years 1964 to 1977 were reviewed. Case reports of Goodpasture's syndrome in the English literature were collected from Index Medicus and other papers cited in these reports up through August of 1977. All available information from each case report was abstracted. In many of the cases some of the data base was not presented and all percentages reported in the present paper are based on only those cases in whom information was available. Summaries of our five cases appear in the "Appendix".

The diagnosis of definite Goodpasture's syndrome was accepted if the following criteria were met: (1) hemoptysis or lung tissue showing pulmonary hemorrhage; (2) clinical or laboratory evidence of renal disease with kidney tissue demonstrating glomerular involvement; and (3) demonstration of anti-GBM antibody by a) linear staining of the glomerular basement membrane with fluorescent-labelled antibodies against human immunoglobulin, b) detection of circulating anti-GBM antibodies in the patient's serum, or c) elution of anti-GBM antibodies from lung and/or kidney tissue. Patients who fulfilled the first two criteria and who did not have immunologic studies documenting the presence of anti-GBM antibodies were considered to have a presumptive diagnosis of Goodpasture's syndrome if the clinical picture and pathologic specimens were sufficient to exclude the presence of renal vein thrombosis with pulmonary embolism, uremia with congestive heart failure, Wegener's granulomatosis, systemic lupus erythematosis, and polyarteritis nodosa.

RESULTS

Fifty cases with a definite diagnosis of Goodpasture's syndrome were discovered in the English literature (2, 8-39) and our files yielded another three cases for a total of 53 patients. All fifty-three had positive linear antibody staining of the glomerular basement membrane demonstrated by direct immunofluorescent studies. Twenty-four of twenty-seven in whom it was measured had detectable circulating anti-GBM antibodies. One hundred eight patients from the literature (1, 40-94) met the criteria for a presumptive diagnosis of Goodpasture's syndrome as did two patients from our files. All together 163 patients form the basis of this report.

Demography. Thirty-eight of the fifty-three subjects with definte Goodpasture's syndrome were male yielding a male to female ratio of 2.5:1. Ninety of the 110 subjects with the presumptive diagnosis of Goodpasture's syndrome were male. The ages of subjects with definite Goodpasture's syndrome ranged from 17 to 65 years with a median age of 23 years (Table I). Seventy percent of the patients were less than 30 years of age at the time of presentation. The decade of most frequent occurrence was the third. The age distribution in subjects with the presumptive diagnosis of Goodpasture's syndrome was similar to those with the definite diagnosis (Table I). Twenty-nine patients (55%) with the definite syndrome were white, one was an Eskimo, and twenty-three patients (43%) were of unspecified race. Fifty-two patients (47%) with the presumptive condition were white, five (5%) were black, one was a Native American, one was of Chinese-Polynesian extraction, and fifty-one (46%) were of unspecified race.

Table I.

Demographic data.

		Definite Diagnosis	Presumptive Diagnosis
SEX	Male	38 (72%)	90 (82%)
	Female	15 (28%)	20 (18%)
	Male:Female	2.5:1.0	4.5:1.0
AGE	Less than 20	14 (26%)	29 (26%)
	20 to 30	23 (43%)	56 (51%)
	Greater than 30	16 (31%)	25 (24%)
	Median age	24	22
RACE	White	29 (55%)	52 (47%)
	Black	0 (0%)	5 (5%)
	Other	1 (2%)	2 (2%)
	Unspecified	23 (43%)	51 (46%)

Symptoms at time of initial presentation (Table II). Forty-three out of fifty (86%) of the patients with a definite diagnosis of Goodpasture's syndrome had pulmonary symptoms at the time of presentation. Thirty-nine patients (78%) had hemoptysis, twenty-three (46%) had dyspnea, and fifteen (30%) had cough, and four (8%) had chest pain. Pulmonary symptoms occurring in the absence of symptoms directly attributable to the urinary system (such as gross hematuria, flank pain, etc.) were reported in thirty-seven patients at the time of onset.

Renal-related symptoms (gross hematuria, edema, and flank pain) were seen less frequently than pulmonary symptoms in patients with a definite diagnosis of Goodpasture's syndrome. Gross hematuria was reported by 10 patients (20%), edema in 5 (10%), and flank pain in one (2%). Renal symptoms co-existed with pulmonary symptoms in six patients. Renal symptoms existed without pulmonary symptoms in five patients.

General symptoms such as fatigue, weakness, and malaise were reported in fourteen cases (28%). Feverishness and/or chills occurred in six cases (12%). Dizziness or syncope was reported by four patients (8%), and gastrointestinal symptoms including anorexia, nausea, vomiting, hematemesis and abdominal pain by nine patients (18%). Sore throat, weight loss, skin rash, arthralgia, and myalgia were rarely reported presentations.

Recent past medical histories of patients with a definite diagnosis of Goodpasture's syndrome included an upper respiratory illness in six cases and intense exposure to organic solvents in six cases. The etiologic agent of upper respiratory illness was not isolated in the six cases and where

Table II.

Presenting symptoms in 50 patients with the definite diagnosis of Goodpasture's syndrome and in 110 patients with the presumptive diagnosis of Goodpasture's syndrome.

Presenting symptoms	Definite	Presumptive
Hemoptysis	39 (78%)	91 (83%)
Dyspnea	23 (46%)	66 (60%)
Cough	15 (30%)	46 (42%)
Fatigue, malaise or weakness	14 (28%)	53 (48%)
Gross hematuria	10 (20%)	17 (15%)
Feverishness and/or chills	6 (12%)	25 (23%)
Anorexia, nausea and/or vomiting	6 (12%)	17 (15%)
Edema	5 (10%)	7 (6%)
Chest pain	4 (8%)	9 (8%)
Syncope or dizziness	4 (8%)	1 (1%)
Sore throat	2 (4%)	7 (6%)
Flank pain	2 (4%)	3 (3%)
Abdominal pain	2 (4%)	2 (2%)
Arthralgia	2 (4%)	1 (1%)
Myalgia	2 (4%)	0 (0%)
Weight loss	1 (2%)	8 (7%)
Hematemesis	1 (2%)	1 (1%)
Skin rash	1 (2%)	0 (0%)
Nasal discharge	0 (0%)	8 (7%)
Polyuria or nocturia	0 (0%)	4 (4%)
Dysuria	0 (0%)	1 (1%)
Diarrhea	0 (0%)	1 (1%)

serologic studies for the presence of streptococcal infection were performed they were negative in 11 of 12 cases. The patients with histories of exposure to organic solvents had occupations or hobbies which involved inhalation of the fumes of solvents such as paint stripper, gasoline, and varnish remover over a period of many months prior to the onset of their illness.

In patients with presumptive diagnoses of Goodpasture's syndromes presenting symptoms occurred at a similar frequency as in those with the definite diagnosis of Goodpasture's syndrome (Table II).

Presenting signs. (Table III) Description of the initial physical examination was available in 33 of the 53 patients with a definite diagnosis of Goodpasture's syndrome. The two most common signs were pallor which was seen in 16 patients (48%) and rales in 12 patients (36%). Of the twenty-five patients who had hemoptysis and whose case reports included the initial physical examination, rales were heard in only eleven (44%). Edema, hypertension, and retinal hemorrhages were observed 12%, 18%, and 6% of patients respectively. Fever was reported in six of the thirty-three patients. Hepatomegaly, splenomegaly, lymphadenopathy, cyanosis, clubbing, and costovertebral angle tenderness were uncommon findings. The presenting features of the clinical examination were similar in patients with a presumptive diagnosis of Goodpasture's syndrome.

Initial laboratory results (Table IV). Chest X-ray examination was performed in forty-three patients with a definite diagnosis of Goodpasture's syndrome. Infiltrates were observed in 35 patients (81%). Twenty-seven

Table III.
Presenting signs in 33 patients with a definite diagnosis of Goodpasture's syndrome and 95 patients with a presumptive diagnosis

Presenting signs	Definite	Presumptive
Pallor	16 (48%)	45 (47%)
Rales	12 (36%)	43 (45%)
Fever (temp. greater than 38°C)	6 (18%)	13 (14%)
Hypertension	6 (18%)	12 (13%)
Edema	4 (12%)	15 (16%)
Heart murmur	4 (12%)	11 (12%)
Fundus abnormalities (retinal hemorrhage)	2 (6%)	4 (4%)
Hepatomegaly	1 (3%)	2 (2%)
Cyanosis	1 (3%)	0 (0%)
Clubbing	1 (3%)	0 (0%)
Lymphadenopathy	1 (3%)	0 (0%)
Splenomegaly	0 (0%)	2 (2%)
Costovertebral angle tenderness	0 (0%)	2 (2%)
Swelling and tenderness of calf	0 (0%)	1 (1%)

Table IV.

Initial laboratory findings in patients with definite and presumptive diagnoses of Goodpasture's syndrome.

Study	Definite Number	%	Presumptive Number	%
Chest X-ray				
Infiltrates	35	81	79	82
No infiltrates	8	19	17	18
Hemoglobin concentration or or hematocrit				
Hgb $\leq$ 10 g/dl or Hct $\leq$ 30 vol%	32	74	82	79
Hgb > 10 g/dl or Hct > 30 vol%	11	26	22	21
Serum iron to iron binding capacity ratio				
Less than 0.16	8	80	8	89
Greater than or equal to 0.16	2	20	1	11
Urinary findings				
Total number of urinalyses	38		100	
>5 rbcs/hpf	27	71	74	74
rbc casts	9	24	11	11
proteinuria	27	71	81	81
normal urinalysis	6	16	12	12
Renal function				
Normal serum creatinine or BUN	13	32	31	37
Serum creatinine = 1.6-5.0 or BUN = 26-70 mg/dl	16	39	25	30
Serum creatinine = 5.1-9.9 or BUN = 71-119 mg/dl	5	12	12	15
Serum creatinine $\geq$ 10 mg/dl or BUN $\geq$ 120 mg/dl	7	17	15	18
Hypocomplementemia				
Total number studied	8		1	
Hypocomplementemic	1	12	0	0
Anti-streptolysin titers				
Total number studied	12		25	
Positive	1	8	2	8
Antinuclear antibodies				
Total number studied	9		3	
Positive	0	0	0	0

out of thirty-two patients with hemoptysis who had a chest X-ray had demonstrable infiltrates. All four patients who presented with dyspnea and/or cough but without hemoptysis had abnormal opacifications on the chest roentgenogram. Three patients who lacked pulmonary signs or symptoms had abnormal chest X-rays. Similar results were observed in the ninety-six patients with a presumptive diagnosis of Goodpasture's syndrome who had chest X-ray examinations.

Moderate to severe anemia (hemoglobin concentration $\leq$ 10 g/dl or hematocrit $\leq$ 30 volumes%) was observed at the time of presentation in thiry-two patients (74%) with a definite diagnosis of Goodpasture's syndrome. The erythrocyte morphology was most often described as hypochromic microcytic and in eight out of ten patients in whom the iron to iron binding capacity ratio was determined the ratio was less than 0.15 suggesting iron deficiency. Twenty-three out of twenty-nine patients (79%) who presented with hemoptysis and had hemoglobin and/or hematocrit measurements were found to have moderate to severe anemia. Three out of four patients with dyspnea and/or cough but without overt hemoptysis had moderate to severe anemia. Three out of seven patients with pulmonary symptoms had hemoglobin concentrations of less than 10 g/dl. Similar results were observed in patients with a presumptive diagnosis of Goodpasture's syndrome with 82 out of 104 (79%) having moderate to severe anemia at the time of presentation.

Urinalysis was performed at the time of presentation in 38 patients with definite Goodpasture's syndrome. Twenty-seven (71%) had hematuria but only nine (24%) had erythrocyte casts. Twenty-seven patients (71%) had proteinuria. Of the six patients who presented with gross hematuria and had

urinalysis results reported all six had proteinuria, but only one was reported to have erythrocyte casts. Thirty-three patients who suffered from hemoptysis, dyspnea, or cough had urine examinations at the time of presentation. Twenty-seven (82%) had an abnormal urinalysis (hematuria, 22; proteinuria, 21, rbc casts, 7). Urine examination was performed in 100 patients with presumptive Goodpasture's syndrome and was normal in twelve, all of who presented with pulmonary symptoms. Hematuria, proteinuria, and erythrocyte casts were noted in 74%, 81%, and 11%, respectively.

Renal function on admission was assessed in 41 patients with definite Goodpasture's syndrome. Thirteen of these patients had a normal serum creatinine ($\leq$1.5 mg/dl) or urea nitrogen ($\leq$25 mg/dl), 16 had creatinine concentration between 1.5 and 5 mg/dl (or BUN = 26 to 70 mg/dl), 5 had creatinine concentrations between 5 and 10 mg/dl (or BUN = 71 to 119 mg/dl), and 7 had a serum creatinine concentration greater than or equal to 10 mg/dl (or BUN $\geq$ 120 mg/dl).

In general the presence of an abnormal urinalysis (>5 red blood cells/hpf, red blood cell casts, >1+ proteinuria) was often associated with the presence of renal impairment. Eighteen out of twenty-seven patients who had abnormal urinalyses had serum creatinine conctrations of greater than 1.5 mg/dl (or BUN >25 mg/dl). In contrast, none of the four patients with a normal urine sediment had elevated serum creatinine or blood urea nitrogen concentrations.

Data on renal function at the time of initial admission were available in eighty-three patients with a presumptive diagnosis of Goodpasture's

syndrome. Thirty-one of the 83 (37%) had normal function, 25 (30%) had serum creatinine concentrations = 1.5 to 5.0 mg/dl (or BUN = 25 to 70 mg/dl), 12 (15%) had creatinine level = 5.1 to 9.9 mg/dl, (or BUN = 71 to 119 mg/dl), 15 (18%) had a serum creatinine concentration of greater than 10 mg/dl or a BUN of greater than 120 mg/dl.

Serum complement was reduced in one out of eight patients with a definite diagnosis of Goodpasture's syndrome. Serologic studies for evidence of streptococcal infection were performed in twelve patients with definite and on twenty-five patients with presumptive Goodpasture's syndrome. Only one patient with definite Goodpasture's syndrome and two patients with the presumptive diagnosis had elevated titers. In patients in whom circulating antinuclear antibodies were sought, the determinations were negative in eight patients with the definite diagnosis and in three patients with the presumptive diagnosis of Goodpasture's syndrome.

Clinical course. Pulmonary abnormalities were the lone presenting features in nineteen patients of whom seven had a definite diagnosis of Goodpasture's syndrome and twelve had a presumed diagnosis. Four of the seven definite Goodpasture's syndrome developed abnormalities in urinalysis of renal function within a month after presentation. Renal function and urinalysis remained normal in the remaining three patients until 4.5 months, 1.5 years, and seven years after initial presentation with pulmonary symptoms. Five of the twelve patients with presumptive Goodpasture's syndrome were discovered to have diminished renal function and/or abnormal urinalyses within a month after presentation while the other seven patients were found to have abnormal renal studies within five months.

Ten patients presented with hematuria or impaired renal function in the absence of pulmonary hemorrhage. Four of these patients had a definite diagnosis of Goodpasture's syndrome while six had a presumptive diagnosis. The four patients with definite Goodpasture's syndrome developed hemoptysis one, three, four, and five weeks after initial admission. The six patients with the presumptive disease demonstrated pulmonary symptoms at two days, one week, three weeks, three months, four months, and two years after initial presentation.

Twenty-six patients (49%) with a definite diagnosis of Goodpasture's syndrome and fifty-three (48%) with a presumptive diagnosis who did not initially present renal failure developed end-stage renal failure. The progression of renal disease in patients with definite Goodpasture's syndrome was usually quite rapid with a median interval from admission to a serum creatinine exceeding 10 mg/dl of five weeks (range 2 days to 11 years). The ultimate progression of the renal disease bore little relationship to the severity of hematuria or proteinuria at the time of initial admission. Yet the ultimate progression of the renal disease to end-stage renal failure did appear related to the degree of renal function impairment at the time of clinical presentation (Table V). Eighty percent of the cases with definite Goodpasture's syndrome and 75 percent with the presumptive diagnosis who had serum creatinine concentrations between 5 and 10 mg/dl or BUN between 70 and 120 mg/dl at onset went on to develop end-stage renal failure resulting in either death or long-term commitment to dialysis. Patients who had serum creatinine concentrations of less than 5.1 mg/dl (or BUN less than 71 mg/dl) had a better renal prognosis although greater than half of the cases also

Table V.

Relationship between ultimate progression to end-stage renal failure and renal function on admission in patients with a definite or presumptive diagnosis of Goodpasture's syndrome. S_{cr} = serum creatinine concentration; BUN = blood urea nitrogen.

Renal function	Definite Diagnosis		Presumed Diagnosis	
	Total number of patients	Number developing end-stage renal failure	Total number of patients	Number developing end-stage renal failure
$S_{cr} \leq 1.5$ mg/dl or BUN ≤ 25 mg/dl	13	8 (62%)	32	21 (66%)
$S_{cr} = 1.6 - 5.0$ mg/dl or BUN = 26 - 70 mg/dl	16	9 (56%)	25	15 (60%)
$S_{cr} = 5.1 - 9.9$ mg/dl ro BUN = 71 - 119 mg/dl	5	4 (80%)	13	10 (77%)
$S_{cr} \geq 10$ mg/dl BUN ≥ 120 mg/dl	7	7 (100%)	15	15 (100%)
No S_{cr} or BUN reported	12	7 (58%)	27	11 (41%)

went on to develop renal failure. There was no difference in the renal outcome between patients with normal renal function on admission and those with only moderately impaired renal function. It is of note that only three of the thirty-three patients with definite Goodpasture's syndrome who had serum creatinine concentrations exceeding 10 mg/dl recovered enough renal function to maintain life without dialysis.

Renal biopsies were obtained in 41 patients with a definite diagnosis of Goodpasture's syndrome (Table VI). Seventeen patients had diffuse (majority of glomeruli involved) extracapillary proliferative changes or diffuse glomerular sclerosis, and eleven of these seventeen patients had or progressed to end-stage renal failure. Seven patients had focal proliferative lesions or mild diffuse mesangial changes, and only two of this group developed renal failure. Five out of six patients whose biopsies revealed areas of necrosis and diffuse proliferative changes progressed to end-stage renal insufficiency. Eleven biopsies were difficult to categorize because of inadequate description of light microscopic morphology although immunofluorescent studies were consistent with Goodpasture's syndrome.

Twenty-three of 53 patients with definite Goodpasture's syndrome were reported to have died (Table VII). In twelve, death occurred secondary to massive pulmonary hemorrhage. Four of the twelve died within one month of admission, seven died between two and six months after presentation, and one died after an unusually long course of eleven years. There was no apparent correlation between renal function at the time of initial presentation and the eventual development of fatal pulmonary hemorrhage (Table VIII).

Table VI.

Summary of renal histology of biopsy specimens obtained from 41 patients with the definite diagnosis of Goodpasture's syndrome and the relationship of renal histology to the development of renal failure.

Glomerular histology	Total number of patients	Number with end stage renal failure (%)
Focal proliferative or mild mesangial changes	7	2 (29%)
Diffuse proliferative or fibrotic changes	17	11 (65%)
Areas of necrosis with diffuse proliferative changes	6	5 (83%)
Unclassified	11	

Table VII.

Causes of Death in Patients with Goodpsture's Syndrome

Definite Diagnosis	Number	Percentage
Pulmonary hemorrhage	12	52
Sepsis (Gram negative)	6	26
Renal failure	2	9
Viral influenza	1	4
Aspergillosis, systemic	1	4
Unknown	1	4
Total	23	

Presumptive Diagnosis	Number	Percentage
Renal failure	35	39
Pulmonary hemorrhage	31	34
Pulmonary hemorrhage and renal failure	13	14
Sepsis (Gram negative)	2	2
Congestive heart failure	2	2
Cerebral hemorrhage	2	2
Epileptic seizure	1	1
Unknown	4	5
Total	90	

Table VIII.

The development of fatal pulmonary hemorrhage as related to renal function at initial presentation in patients with the definite diagnosis of Goodpasture's syndrome. S_{cr} = serum creatinine concentration; BUN = blood urea nitrogen concentration.

Renal function	Total number	Number dying from pulmonary hemorrhage
$S_{cr} \leq 1.5$ mg/dl or BUN $\leq$ 25 mg/dl	13	2 (15%)
S_{cr} = 1.6 - 5.0 mg/dl or BUN = 26 - 70 mg/dl	16	5 (31%)
S_{cr} = 5.1 - 9.9 mg/dl or BUN = 71 - 119 mg/dl	5	1 (20%)
S_{cr} = 10 mg/dl or greater BUN = 120 mg/dl or greater	7	2 (29%)
No initial S_{cr} or BUN reported	12	2 (17%)

Nevertheless, of the thirty-five patients who eventually developed end-stage renal failure, eleven died of pulmonary hemorrhage (Table IX). In contrast, only one of eighteen patients who maintained adequate renal function to sustain life died of pulmonary hemorrhage. In six patients the cause of death was attributable to gram negative bacterial sepsis. Five of these six patients received steroids and/or immunosuppressive agents at the time of onset of the signs of sepsis. In only two cases was the cause of death directly attributable to renal failure. No discernable correlation was observed between the degree of renal insufficiency on initial admission and eventual progression to death from all causes (Table X).

Ninety of the 110 patients (82%) in the presumptive Goodpasture's syndrome group were reported to have died (Table VII). A striking difference in the cause of death between this group and the definite Goodpasture's syndrome was observed. Whereas death secondary to end-stage renal failure occurred in only two out of the 23 patients with a definite diagnosis of Goodpasture's syndrome, renal failure accounted for 47 out of 90 deaths in the group with presumed Goodpasture's syndrome. Causes of death not observed in the group with definite Goodpasture's syndrome included congestive heart failure (2 patients), cerebral hemorrhage (2 patients), and epileptic zeizure (1 patient).

Thirty of the 53 patients with definite Goodpasture's syndrome were alive at the time of publication of their case reports. Twenty-three of these 30 patients had follow-up of greater than six months after clinical presentation. Of these twenty-three patients eight were on chronic hemodialysis and

Table IX.

The development of fatal pulmonary hemorrhage as related to the development of end-stage renal failure in patients with the definite diagnosis of Goodpasture's syndrome.

	Total number	Fatal pulmonary hemorrhage
Renal failure during course of illness	35	11 (31%)
No renal failure	18	1 (6%)

Table X.

Relationship between renal function at presentation and death. S_{cr} = serum creatinine concentration; BUN = blood urea nitrogen concentration.

	DEFINITE DIAGNOSIS		PRESUMPTIVE DIAGNOSIS	
	Total number	Number dead	Total number	Number dead
S_{cr} = 1.5 mg/dl or less, BUN = 25 mg/dl or less	13	6 (46%)	31	20 (64%)
S_{cr} = 1.6 - 5.0 mg/dl or BUN = 26 - 70 mg/dl	16	8 (50%)	25	23 (92%)
S_{cr} = 5.1 - 9.9 mg/dl or BUN = 71 - 119 mg/dl	5	2 (40%)	12	10 (83%)
S_{cr} = 10.0 mg/dl or greater, BUN = 120 mg/dl or greater	7	3 (43%)	15	14 (93%)
No S_{cr} or BUN reported at time of presentation	12	4 (33%)	27	25 (93%)

two had functioning renal transplants. Six were clinically well with mild diminution of renal function and seven were described as alive and in good health. Ultimate survival was closely related to changes observed on renal biopsy (Table XI). Twenty of the 110 patients with a presumptive diagnosis of Goodpasture's syndrome survived. Two of these 20 patients had received functioning renal transplants, one was on chronic hemodialysis, and seventeen were described as having no or moderate abnormalities in renal function.

Therapy. One of the most important aspects in the therapy of Goodpasture's syndrome has been the use of dialysis in the treatment of renal failure (fig. 1). Of 107 patients with a definite or presumptive diagnosis of Goodpasture's syndrome who developed renal failure during the course of illness, 63 patients received either peritoneal dialysis or hemodialysis. Of the patients who did not receive dialysis, only seven percent survived in contrast to 27% of the dialysed patients.

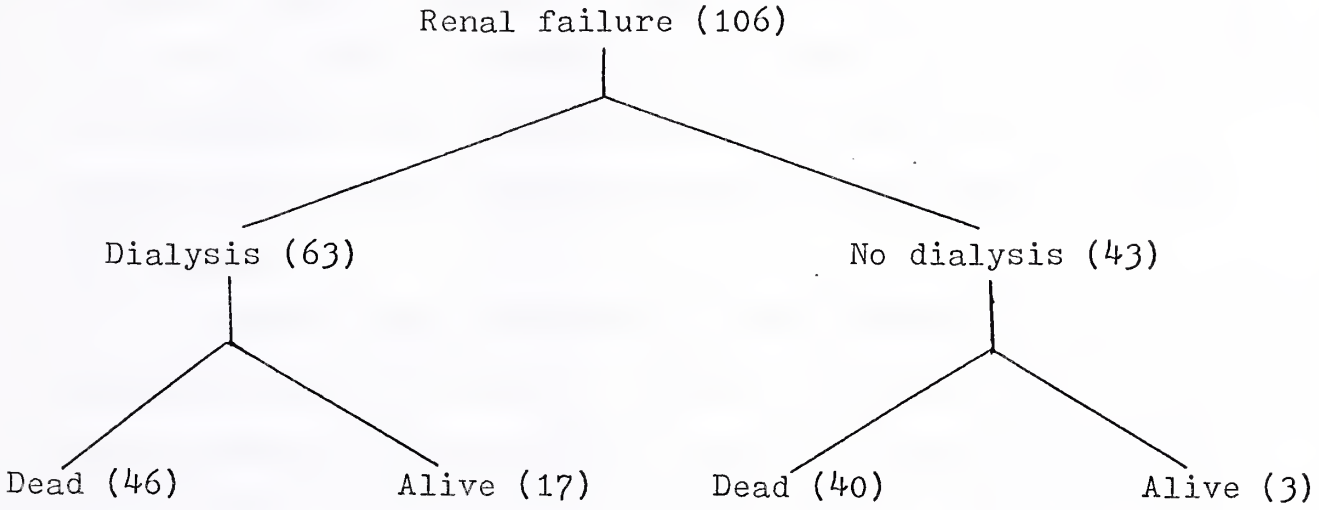
In addition to supportive treatment with dialysis, a number of therapeutic regimens have been employed in Goodpasture's syndrome. These have included 1) corticosteroids (hydrocortisone, methylprednisolone, prednisone, and dexamethasone) most frequently given at a dose equivalent to 60 mg of prednisone per day over several weeks with tapering to a maintenance dose after symptoms subsided, 2) immunosuppressive agents (azathioprine, cyclophosphamide, nitrogen mustard, and mercaptopurine) with azathioprine the most commonly used agent, 3) nephrectomy (with or without splenectomy), and 4) plasmapheresis combined with immunosuppressive agents with or without steroids.

Table XI.

Survival in patients with a definite diagnosis of Goodpasture's syndrome as related to histology of renal biopsy specimens.

Glomerular histology	Total number	Greater than 6 months' survival with minor or no decrease in renal function
Focal proliferative or mild mesangial changes	7	6 (86%)
Diffuse proliferative (extracapillary) or diffuse fibrotic changes	19	1 (5%)
Unclassified histology	13	7 (54%)

Figure 1.
Effect of dialysis on patient survival in Goodpasture's syndrome.



The survival of patients with a definite or presumptive diagnosis of Goodpasture's syndrome as related to treatment modality is summarized in Table XII. The survival of patients treated with steroids alone (18%) was similar to patients treated with supportive therapy (11%). The survival of patients treated with immunosuppressive agents (52%), nephrectomy (73%), or plasmapheresis (80%) was higher than either steroids or supportive therapy. One patient received anticoagulation with supportive therapy and survived.

An important factor contributing to the differences in survival between groups was the use of dialysis. Whereas all patients treated by nephrectomy, and all patients who needed dialysis who were treated by plasmapheresis received dialysis, 91 percent of patients treated by immunosuppressive agents who needed dialysis received dialysis, 53 percent of those patients treated with steroids received dialysis, and 29 percent of those treated with supportive therapy only were dialysed.

The development of renal failure also differed between the treatment groups (Table XIII). While 59 percent of patients who received supportive therapy and 68 percent of steroid-treated patients eventually developed renal insufficiency, only 17 percent of patients treated with plasmapheresis and 52 percent of patients who received immunosuppressive therapy developed renal insufficiency.

Table XII.

The effect of therapy on survival in patients with definite and presumed diagnoses of Goodpasture's syndrome

	Treatment				
	Supportive	Steroids	Immunosuppression	Nephrectomy	Plasmapheresis
Survivors	6 (11%)	10 (18%)	15 (52%)	11 (73%)	8 (80%)
Non-survivors	48 (89%)	45 (82%)	14 (48%)	4 (27%)	2 (20%)

Table XIII.

The development of renal failure as related to therapy in patients with a definite or presumptive diagnosis of Goodpasture's syndrome.

Therapy	Total number	Number developing renal failure
Supportive therapy	44	26 (59%)
Steroids	37	25 (68%)
Immunosuppression	21	10 (48%)
Plasmapheresis	6	1 (17%)

DISCUSSION

Patients with a definite diagnosis of Goodpasture's syndrome had a similar clinical presentation to those with a presumptive diagnosis, suggesting that most of the cases with a presumptive diagnosis were indeed correctly diagnosed as having Goodpasture's syndrome. Hemoptysis and rales with infiltrates on chest roentgenogram, iron deficiency anemia, and an abnormal urinalysis with diminished renal function were the major presenting features. Presentation with either renal manifestations (6%) or pulmonary manifestations (12%) alone was uncommon.

Direct immunofluorescent staining of renal tissue was performed on biopsy or autopsy material in all patients included in the definite Goodpasture's syndrome group. The staining was considered positive for the demonstration of anti-GBM antibodies if a strong, smooth, linear distribution of immunofluorescence was observed. Although positive direct staining of the glomerular basement membrane has occasionally been described in patients with systemic lupus erythematosis (96) and diabetic glomerulopathy (97, 98), these conditions were easily excluded by the clinical history, laboratory studies, and renal histology.

Techniques used to measure circulating anti-GBM antibodies in the present case studies included radioimmunoassay, hemagglutination, indirect immunofluorescent, and gel immunoprecipitation studies (99, 100). These assays for the detection of circulating anti-GBM antibodies were not quite as sensitive as direct immunofluorescent studies performed on renal tissue. Of the twenty-seven patients who were tested for circulating anti-GBM

antibodies and in whom direct immunofluorescent studies were also performed on renal tissue, three had no measurable circulating anti-GBM antibodies. If the diagnosis of Goodpasture's syndrome is being entertained and tests for circulating anti-GBM antibodies are negative, a renal biopsy with direct immunofluorescent staining should be performed. Lung tissue was examined for the presence of linear staining of the alveolar capillary basement membrane in thirteen patients (three biopsy and ten post mortem specimens). Only eight specimens (two biopsy, six post mortem) revealed positive linear immunofluorescent staining. All thirteen patients had positive linear staining on renal biopsy or autopsy specimens. These results suggest that lung biopsy is a less reliable method of establishing the diagnosis of Goodpasture's syndrome although a large number of cases have not been studied. Nevertheless, in circumstances in which other primary pulmonary processes (i.e., infection, tumor, etc.) are being considered in the differential diagnosis along with Goodpasture's syndrome, a lung biopsy may be the procedure of choice.

The renal biopsy may also provide useful information concerning the eventual development of end-stage renal failure and death. While only 29 percent of patients with focal proliferative or mild mesangial changes went on to end-stage renal insufficiency, 70 percent of patients with diffuse crescentic proliferative changes eventually developed chronic renal failure. Five out of six patients with diffuse proliferative lesions and necrosis developed renal failure.

Survival also correlated closely with renal histology. Eighty-six

percent of patients with focal or mild mesangial lesions were living at the time their cases were reported. This was in contrast to only five precent of patients with diffuse proliferative lesions.

The degree of impairment of renal function on admission also bore a close relationship to the development of end-stage renal failure and eventual death. Whereas 64 percent (29/45) of patients with normal renal function on admission progressed to renal insufficiency, 90 percent (36/40) of patients with a serum creatinine concentration greater than 70 mg/dl developed end-stage renal failure. Mortality was higher in patients with advanced renal failure on admission (77%) compared with those with normal renal function (59%) if one combined the data from the definite and presumed Goodpasture's syndrome groups. Another interesting relationship was that between renal failure and pulmonary hemorrhage. Although there was no correlation between the development of fatal pulmonary hemorrhage and renal function on admission (Table VIII), the development of renal failure was associated with a striking increase in fatal pulmonary hemorrhage (Table IX). Only one out of 18 (6%) patients without renal failure succumbed to pulmonary hemorrhage while 11 out of 35 (31%) patients with renal failure died of pulmonary hemorrhage. Although nephrectomy has been advocated as a life-saving measure for massive pulmonary hemorrhage, two of the 15 patients in whom nephrectomy was performed eventually died from pulmonary hemorrhage.

The prognosis as well as the cause of death in patients with Goodpasture's syndrome has changed considerably over the last decade. The majority of cases with a presumptive diagnosis of Goodpasture's syndrome was

reported before 1965 at a time when immunofluorescent techniques for the determination of anti-GBM antibodies were not readily available. In this group 90 of 100 (82%) died and the leading cause of death was renal failure (Table VII). In contrast, only 23 out of 53 (43%) with a definite diagnosis of Goodpasture's syndrome died and renal failure accounted for only 9 percent of this group (Table VII). A major difference influencing the eventual outcome and cause of death between these groups of patients appeared to be the availability of dialysis. While end-stage renal failure occurred with equal frequency in both groups only 39 percent of patients with a presumptive diagnosis who needed dialysis actually received dialysis compared to 94 percent with a definite diagnosis. As can be seen in figure 1, 27 percent of patients treated with dialysis survived compared to only 7 percent who were not dialyzed.

Because of the infrequent occurrence of Goodpasture's syndrome and its poor prognosis, controlled prospective studies examining different modalities of therapy have not been feasible. Therefore, caution must be exercised in interpreting the results of therapeutic intervention in this disease. Steroids in conventional doses (40 to 80 mg of prednisone per day or its equivalent) appeared to have little benefit over supportive therapy alone. High doses of steroids (e.g., methyl prednisolone 1 gram every 8 hours) may be more effective although only a few patients have been reported who have received such therapy (20). Immunosuppressive therapy in combination with steroids was associated with a higher survival rate (52%) than in the group treated with steroids alone (18%) (Table XIII). However, dialysis was employed with greater frequency in patients treated with immunosuppressive

agents (91%) than in patients treated with steroids alone (53%). Whether the increased survival was attributable to treatment per se or to the greater availability of dialysis cannot be determined. It should be noted, however, that 68 percent of the steroid treated group progressed to renal insufficiency compared to 48 percent of patients treated with immunosuppressive agents.

The best results were obtained in patients treated with bilateral nephrectomy or plasmapheresis, approximately three-quarters of the patients surviving in both groups. Interpretation of the results obtained with nephrectomy is made difficult by the small numbers of patients receiving nephrectomy and by the decisions surrounding the application of this mode of therapy in the individual patient. At least two factors must be present if nephrectomy is to be performed: 1) the patient must be stable enough to endure the operation and 2) chronic dialysis facilities must be available to the patient. The most efficacious therapy would be one that not only prevents pulmonary hemorrhage but also prevents the development of renal failure. Obviously, nephrectomy does not achieve the latter goal and whether it prevents pulmonary hemorrhage must be questioned since at least two patients have been reported who died of massive pulmonary hemorrhage after nephrectomy.

Most recently, plasmapheresis has been advocated in the treatment of Goodpasture's syndrome (21- 23, 38). Of the ten with this modality, eight have survived and only one out of six patients progressed from normal or moderately diminished renal function to renal failure. The rationale behind the use of plasmapheresis is to remove directly those circulating

antibodies which are responsible for the renal and pulmonary damage. Although the results to date seem encouraging and plasmapheresis seems to be a relatively safe procedure, it should be noted that all patients treated with plasmapheresis have also received steroids and/or immunosuppressive agents. In addition, the correlation between circulating anti-GBM antibodies and the improvement in pulmonary hemorrhage and renal function has been poor (23). If plasmapheresis proves to be beneficial, it remains to be determined whether its efficacy is based upon removal of circulating anti-GBM antibodies or upon removal of other mediators of the host response.

In summary, maintenance dialysis for those patients who develop renal failure appears to be an important factor for the improved outlook in patients with Goodpasture's syndrome. Conventional doses of steroids seem to be without effect on either long-term survival or preservation of renal function. Although the outcome in patients treated with immunosuppressive and/or cytotoxic agents is slightly better than those treated with supportive therapy or steroids alone, the efficacy of these agents remains to be proven. The results of nephrectomy are similar to those obtained with plasmapheresis. Since nephrectomy can be expected to have a significant incidence of morbidity and mortality in this patient population and since nephrectomy automatically commits the patient to life long dialysis, plasmapheresis may be a better therapeutic option. It should be clearly understood, however, that plasmapheresis is still of unproven benefit at the present time. Because of the infrequent occurrence of Goodpasture's syndrome a controlled study involving several institutions would be necessary to provide the information necessary for determining the efficacy of the various modes of therapy in this condition.

APPENDIX

Case 1:

This 51-year old female first presented at Yale-New Haven Hospital with a six month history of coughing up bright red blood. She denied feverishness, chills, night sweats, and weight loss. Past history included exposure to tuberculosis and to irritating fumes at the electrician's shop where she worked. She also had been followed at the orthopedic clinic because of arthralgias due to osteoarthropathy. On admission the physical examination was unremarkable except for swelling and tenderness along the course of the greater saphenous vein. Her hematocrit was 28 vol%, hemoglobin concentration 8.7 g%, WBC 9800 with normal differential. BUN was 12 mg/dl, serum electrolytes were normal, serum iron 13 mg/dl, serum iron binding capacity 373 µg/dl, total protein 6.8 g/dl, albumin 3.7 g/dl. Prothrombin and partial thromboplastin time were within normal limits. Liver function tests were normal. EKG was also within normal limits. Arterial blood pO_2 was 84 torr and pCO_2 36 torr. Chest x-ray was unremarkable as was pulmonary angiography and bronchography. Bronchoscopy revealed blood in the right middle lobe and right lower lobe bronchial orifices. Sputum cultures and cytology were negative. PPD was non-reactive. One urinalysis during her first week of hospitalization revealed 2 to 10 rbc's/hpf and 1+ proteinuria. Four others were normal or contaminated. The patient's superficial thrombophlebitis resolved and her hemoptysis gradually decreased. She was discharged on ferrous sulfate (300 mg three times a day orally).

She continued to have intermittent periods of production of blood-tinged sputum and developed parasternal chest discomfort occurring at rest and upon exertion and was closely followed in the chest clinic until six months after her initial admission when she was re-admitted because of continued hemoptysis, chest pain, and weakness. Urinalysis revealed 3+ proteinuria and 20 rbs/hpf. BUN was 28 mg/dl and serum creatinine concentration was 2.5 mg/dl. Chest roentgenogram showed right lower lobe and left lower lobe ground glass densities. An open lung biopsy was performed and showed intra-alveolar hemorrhage and scarring. Renal histology of a sample obtained by percutaneous biopsy was markedly distorted with many hyalinized glomeruli, and marked epithelial proliferation and areas of necrosis in the remaining glomeruli. During her admission hemoptysis ceased prior to the onset of treatment with prednisone (10 mg daily) and azathioprine (100 mg/day).

This patient has been followed in renal-metabolism clinic for the past 11 years over which time she has become hypertensive and has gradually lost renal function. At last visit to the clinic, she was feeling well on her therapy consisting of azathioprine (100 mg daily), hydrochlorthiazide, sodium bicarbonate and amphogel. Her serum creatinine concentration is 8.5 mg/dl, sodium 140 meq/l, potassium 5.2, chloride 100, bicarbonate 18.3. Her calcium was 8.6 mg/dl and phosphorus 7.4. Urinalysis revealed 2+ proteinuria, 10-20 rbc's/hpf, and 1-3 wbcs/hpf.

Case 2:

This 51-year-old white male was admitted to Yale-New Haven Hospital because of weakness, left flank pain, nausea, vomiting, and diarrhea for three weeks. He stated that he was healthy all his life except for hypertension which had been discovered two years before this admission. Three weeks prior to admission the patient developed intermittent nausea, vomiting, anorexia, diarrhea, and generalized weakness. He also suffered from left flank pain which increased with respiration and was associated with nocturia but not dysuria. The patient saw his private physician one week prior to admission at which time a urinalysis revealed hematuria. The patient was instructed to rest in bed and to take anti-emetic medications. At first he felt better and even returned to work but three days before admission the flank pain and fatigue returned. He denied cough, hemoptysis, skin rashes, and sore throat. Family members noticed that the patient had puffy eyes for about two weeks. The patient was admitted for further evaluation and treatment.

Physical examination revealed a middle-aged man in no acute distress. BP 190/110, pulse rate 92 regular, temperature 99°F, respiratory rate 18. He had 1+ periorbital edema. A-V nicking but no hemorrhages or exudates were noted on fundoscopic examination. His chest was clear. He had left flank tenderness. Laboratory studies: hemoglobin concentration was 10 g/dl, hematocrit 32 vol%, WBC 6,700 (normal differential). Serum glucose was 75 mg/dl, BUN 60 mg/dl, creatinine 9.5 mg/dl, sodium 140 meq/l, potassium 6.1, chloride 104, and bicarbonate 18.4. Urinalysis revealed a specific gravity of 1.011, 3+ proteinuria, 5-6 wbcs/hpf, and numerous rbcs/hpf.

Initial chest x-ray demonstrated a slightly enlarged heart with clear lung fields. The patient's serum iron concentration was 55 µg/dl and iron binding capacity was 323 µg/dl. A twenty-four hour urine collection and protein determination revealed a protein excretion rate of 3.5 g/24 hours.

Two days after admission the patient developed severe hemoptysis which was associated with perihilar alveolar-type infiltrations on chest x-ray. A renal biopsy was performed. Light microscopic examination of the tissue showed chronic and active focal necrotizing glomerulonephritis with crescents affecting all glomeruli and some interstitial scarring. He was treated with prednisone (40 mg daily) and azathioprine (100 mg daily) as well as with peritoneal and hemodialysis. Despite therapy the patient died 18 days after admission as a result of acute respiratory insufficiency and hyperkalemia.

Case 3:

This 21-year-old white female, one pack-per-day smoker was admitted to a community hospital because of fatigue, malaise, and anorexia beginning three weeks prior to admission, gross painless hematuria starting two weeks before admission, nausea and vomiting with flank discomfort one week prior to admission, and hemoptysis and dyspnea for three days. The patient reported intermittent cough productive of small amounts of blood for 6 months. Physical examination at initial presentation was unremarkable. Laboratory studies revealed a hemoglobin of 12 g/dl and a hematocrit of 36 vol%. Her BUN was 12 mg/dl, serum creatinine 1.1 mg/dl. Antinuclear antibody, ASLO titers and C_3 studies were all within normal limits. Urinalysis revealed numerous red blood cells. Chest roentgenogram showed a diffuse miliary infiltrate. An intravenous pyelogram was read as normal. Cystoscopy revealed bleeding from both ureteral orifices. Bronchoscopy showed no focal source of bleeding. Within one week after admission she became acutely dyspneic and pale and developed diffuse rales on examination. She was subsequently transferred to Yale-New Haven Hospital for further evaluation and treatment.

On admission the patient appeared acutely ill, dyspneic and pale. Her pulse was 130, respiratory rate 45, temperature 99°F, and BP 120/50. She had diffuse rales and rhonchi and 1+ pretibial edema. Her hemoglobin concentration was 4.7 g/dl, hct 14.7 vol%, WBC 9,900 (70 segs, 2 bands, 17 lymphocytes, 8 monocytes, 3 eosinophils), 140,000 platelets. Urinalysis: specific gravity 1.006, pH 6.0, 2+ proteinuria, numerous rbcs/hpf, 6-8 wbcs/hpf. Her BUN was 60 mg/dl, serum creatinine 7.0 mg/dl, sodium 129 meq/l,

potassium 5.1, chloride 102, and bicarbonate 16. Serum protein was 4.9 g/dl and albumin 2.4 g/dl. ASLO titer was 250. Rheumatoid factor, antinuclear antibody, prothrombin time and partial thromboplastin time were within normal limits.

Because of the severity of hemoptysis several transfusions with leukocyte poor blood were required to keep the patient's hematocrit above 20 vol%. Peritoneal and hemodialysis were performed beginning the first week after admission because of renal insufficiency (serum creatinine exceeding 10.0 mg/dl). The patient's course was complicated by peritonitis treated with antibiotics, by staphylococcal parotitis, by left retinal artery occlusion, and by periods of hypotension and thrombocytopenia. Despite treatment with blood and platelet transfusions, prednisone (60 mg daily), azathioprine (100 mg daily), antibiotics, and mechanical respiratory assistance, the patient became comatose and died one month after admission.

At post mortem examination the patient was found to have widespread aspergillosis with fungal elements in the central nervous system, lung, peritoneal cavity and myocardium. She had multiple gastric ulcers with evidence of gastrointestinal hemorrhage, left retinal artery occlusion, massive pulmonary hemorrhage with hemosiderosis and diffuse crescentic glomerulonephritis with necrosis of capillary tufts and early hyalinization of glomeruli. There was linear deposition of IgG on glomerular and pulmonary capillary basement membranes as detected by direct immunofluorescent studies.

Case 4:

This 24-year-old white man was in excellent health until two years prior to his admission to this hospital at which time he presented to another hospital with cough with hemoptysis (1/2 cup per day), myalgias, and arthralgias. He was reported to have had a normal physical examination. Laboratory investigations revealed a hemoglobin concentration of 9 g/dl, sedimentation rate of 40, a serum iron concentration of 7 µg/dl, an elevated rheumatoid factor of 512, and an abnormal chest x-ray revealing bilateral patchy infiltrates. An open lung biopsy was subsequently performed. Examination of the biopsy specimen by light microscopy showed intra-alveolar hemorrhage, thickened alveolar septae, and hemosiderin-laden macrophages. The patient was started on prednisone (150 mg daily). Hemoptysis, arthralgias, and myalgias subsequently terminated and the hemoglobin concentration returned to normal levels.

The patient did well until one year later when he again presented with hemoptysis. He also had a nodular lesion on his left elbow. The histology of a biopsy specimen of the nodular lesion was thought to be consistent with that of a rheumatoid nodule. He did well after re-institution of high dose prednisone therapy.

Six months later the patient again suffered from a recurrence of hemoptysis. He was started on prednisone and azathiprine which resulted in subsidence of hemoptysis.

He was referred to Yale-New Haven Hospital for further evaluation six months later. On admission, except for a Cushingoid appearance, the physical examination was within normal limits. His hemoglobin level was 11.9 g/dl,

hematocrit 34 vol%, WBC 13,800 (85 segs, 2 bands, 8 lymphocytes, 4 monocytes, 1 metamyelocyte). Urinalysis disclosed a specific gravity of 1.019, 1+ proteinuria, 0-1 wbc/hpf, 5-8 rbcs/hpf. Serum creatinine concentration was 0.9 mg/dl, BUN 25 mg/dl, sodium 139 meq/l, potassium 5.0, chloride 104, and bicarbonate 26. Creatinine clearance was 117 ml/min. Prothrombin and partial thromboplastin times were normal. Serum complement (C_3) level was normal. Rheumatoid factor was negative. Chest x-ray showed blunting of the right costophrenic angle with a slight increase in density of the right lower lobe. IVP was within normal limits. Sputum smears and cultures were negative for acid fast organisms. Light microscopy of percutaneous renal biopsy specimen revealed twenty-five glomeruli showing various degrees of hypercellularity, focal segmental necrosis and active epithelial crescent formation in over half of the glomeruli. Electronmicroscopy showed some collapse of the basement membrane but no electron dense deposits. Direct immunofluorescent staining showed a linear pattern for IgG within the glomeruli and granular deposits of IgG within the mesangial matrix. The patient was discharged and treated with prednisone (100 mg daily).

One month after discharge he developed a skin rash which was biopsied and revealed a leukocytoclastic angiitis. The rash resolved shortly after treatment with methotrexate (50 mg/week) was instituted. Since that time until the present (over 2 1/2 years after initial presentation, he has been asymptomatic but continues to have 2+ proteinuria and 3-5 rbcs/hpf.

Case 5:

This 47-year-old white male was admitted to a community hospital because of left upper quadrant abdominal pain, guaiac positive stools and abnormal chest x-ray. Ten days prior to admission he began to experience early satiety. Three days prior to admission he developed left upper quadrant pain which was accentuated by deep inspiration. He denied hemoptysis, melena, hematemesis, and hematochezia. Past medical history was significant for peptic ulcer disease nine years before admission.

Physical examination showed a pale, white middle-aged man in no acute distress. Temperature was 99°F, blood pressure 110/70, pulse 88, respiratory rate 12 per minute. The remainder of the physical examination was unrevealing except for 2+ guaiac positive stools.

Laboratory studies: Hemoglobin concentration was 8.0 g/dl, hematocrit 27 vol%, WBC 8,100 (68 polys, 1 band, 3 eosinophils, 25 lymphs, 2 atypical lymphs, and 1-2 nucleated rbcs/100 wbcs). Platelets appeared adequate in number. Reticulocyte count was 10.8%. Urinalysis revealed a specific gravity of 1.024, pH 6.0, protein 30 mg/dl, 10-20 rbcs/hpf, no casts. BUN was 10 mg/dl, serum creatinine 1.6 mg/dl, sodium 137 meq/l, potassium 4.0, chloride 102, bicarbonate 25. Serum iron concentration was 40 µg/dl and a serum iron binding capacity 364 µg/dl. Sputum showed hemosiderin-filled macrophages. ANA, LE prep, and ASOT studies were within normal limits. Chest x-ray showed extensive alveolar infiltrates in the right lower lobe and right middle lobe. Pulmonary function tests were consistent with moderate restrictive disease with reduced maximum voluntary ventilation. Arterial blood gas determinations revealed a pH of 7.48, pCO_2 of 33 mmHg, and pO_2 of

66 mmHg. Upper GI barium studies demonstrated a deformity of the duodenal bulb but no ulcer. IVP was within normal limits. A twenty-four hour urine collection revealed a protein excretion rate of 2 g/24 hours.

Over the next two weeks, the patient experienced progressive deterioration of renal function with BUN concentrations going to 77 mg/dl and creatinine concentrations to 5.6 mg/dl. In addition he experienced two episodes of hemoptysis. He was started on prednisone 80 mg daily and was then transferred to Yale-New Haven Hospital for further evaluation and consideration of additional therapy.

Physical examination at Yale-New Haven Hospital revealed an afebrile white male with mild respiratory distress. Respiratory rate was 25 per minute, blood pressure 130/80, and pulse 72. He had diffuse rales bilaterally. His admission BUN concentration was 92 mg/dl and creatinine concentration was 10.0 mg/dl. Over the next two weeks the serum creatinine concentration increased to 13 mg/dl. He underwent peritoneal dialysis and was begun on azathioprine (75 mg daily) along with prednisone (60 mg daily). A renal biopsy was performed and light microscopic examination of the specimen revealed severe necrotizing and crescentic glomerulonephritis. Direct immunofluorescent studies demonstrated linear deposition of IgM along the glomerular basement membrane. Three days after peritoneal dialysis was initiated the patient had a spontaneous diuresis. Shortly thereafter (3 weeks after transfer) he was discharged on prednisone (60 mg daily), azathioprine (75 mg daily) and antacids.

Over the next two years he was followed in the renal-metabolism clinic. His prednisone was gradually tapered over a period of eighteen months. He

was maintained on azathioprine (100 mg daily) and his antacids. His BUN and serum creatinine concentrations fell to 41 and 2.8 mg/dl, respectively.

Thirty months after the onset of illness the patient was admitted for right upper quadrant abdominal pain, leukocytosis, and fever. He was found to have a ruptured appendix at operation. He tolerated the procedure well.

Three years and five months after his initial presentation the patient was noted to have gradual deterioration of renal function despite azathioprine therapy (100 mg daily). His serum creatinine concentration was 4.1 mg/dl at that time. A renal biopsy was performed which revealed severe interstitial and glomerular fibrosis. A minority of glomeruli were well-preserved and others showed persistent proliferative changes.

Four months later he developed shortness of breath and diminished exercise tolerance. His hematocrit was found to be 10 vol%. He was transfused and started on digoxin. A good clinical response was observed.

This patient's final admission occurred three years and eleven months after the onset of his illness. He was admitted because of a one day history of gross hemoptysis. He was in mild respiratory distress and had rales at both bases. His BUN concentration was 143 mg/dl and serum creatinine was 12.5 mg/dl. His hemoglobin concentration was 4.7 g/dl, hematocrit 15 vol%, and WBC 8,300 (81 segs, 9 bands, 10 lymphs). Urinalysis demonstrated 3+ proteinuria and numerous red blood cells. Arterial blood gas determinations indicated a pH of 7.43, pO_2 of 46 mmHg and pCO_2 of 20 mmHg. He experienced rapid clinical deterioration with the development of respiratory failure, GI bleeding, staphylococcal pneumonia, and Pseudomonas and staphylococcal sepsis despite aggressive management with mechanical ventilatory assistance

(with positive end-expiratory pressure), intensive antacids, antibiotics, methylprednisolone (250 mg every six hours), cyclophosphamide (150 mg daily), and peritoneal dialysis. The patient died twelve days after admission of massive gastrointestinal hemorrhage, sepsis and his underlying disease.

At autopsy he was found to have pulmonary hemorrhage and hemosiderosis with bilateral interstitial and bacterial pneumonias, and pleural effusions. Staphylococcus aureus and Pseudomonas aeruginosa were cultured from blood and lung tissue. Multiple ulcers in the stomach, duodenum, and colon were also found. The kidneys showed bilateral cortical scarring with marked hydronephrosis. Microscopic examination of the kidneys revealed diffuse interstitial fibrosis, generalized diffuse glomerulosclerosis with mesangial thickening and scarring in a segmental distribution in the remaining glomeruli. Direct immunofluorescence studies revealed no deposition of immunoglobulins along the glomerular basement membrane. The urinary bladder was trabeculated and there was a prominent medial lobe of the prostate.

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