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Alveolar Hemorrhage Associated with Glomerulonephritis So-called Pulmonary Renal (Goodpasture's) Syndrome

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Goodpasture's syndrome is characterized by pulmonary associated with renal abnormalities and a group of systemic diseases share immunopathogenic mechanisms which is an autoimmune anti-glomerular basement membrane disease. Pulmonary renal syndrome is rather common in the western countries, but rare in Japan. The present two cases showed clinical and pathological features of rapidly progressive glomerulonephritis complicated with massive pulmonary hemorrhage. Most of the hemorrhage appeared acute with intact red blood cells in alveolar spaces, and also had variable numbers of hemosiderin-laden macrophages as an evidence of old hemorrhage. In one case of Goodpasture's syndrome, linear deposits of IgG were demonstrated in alveolar walls, glomerular capillary, Bowman's capsular basement membrane, and tubules of kidneys. These evidences indicate the present two cases to be the so-called Goodpasture's syndrome.

Introduction

The association of glomerulonephritis and hemorrhagic pneumonitis was first described by Goodpasture in 1919. Goodpasture's syndrome is typically associated with a dramatic course characterized by rapid loss of renal function and asphyxia, which is traditionally considered to be a singles-phase illness characterized by the loss of renal function, death from lung hemorrhage, or rarely, complete recovery. Goodpasture's syndrome, characterized clinically as glomerulonephritis associated with pulmonary hemorrhages, can be more narrowly defined immunopathologically as antibody against glomerular basement membrane and antialveolar basement membrane disease. It is generally accepted that antibasement membrane antibodies are directly involved in the initiation and the development of glomerulonephritis and pulmonary hemorrhage. The clinical features of intrapulmonary hemorrhage with hemoptysis, anemia, and radiologic evidence of lung infiltrates associated with glomerulonephritis are linked by pathogenetic definition in the disease entity known as Goodpasture's syndrome. Immunohistochemical studies demonstrated a linear deposition of IgG along the glomerular basement membrane as well as the alveolar basement membrane (Beechler *et al.*, 1980; Beirne *et al.*, 1968; Hogan *et al.*, 1978; Koffler *et al.*, 1969; Kondo *et al.*, 1986; Lombard and Colby, 1989; Sturgill and Westervelt, 1965).

The present paper describes two autopsy cases of the so-called Goodpasture's syndrome as intrapulmonary hemorrhage (Fig. 1) and glomerulonephritis (Fig. 2).

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Fig. 1. On the cut surface of the lung, hemorrhages, pneumonia, and fibrosis were observed.

Fig. 2. On the cut surface of the kidney, finely granular nephrosclerosis was seen

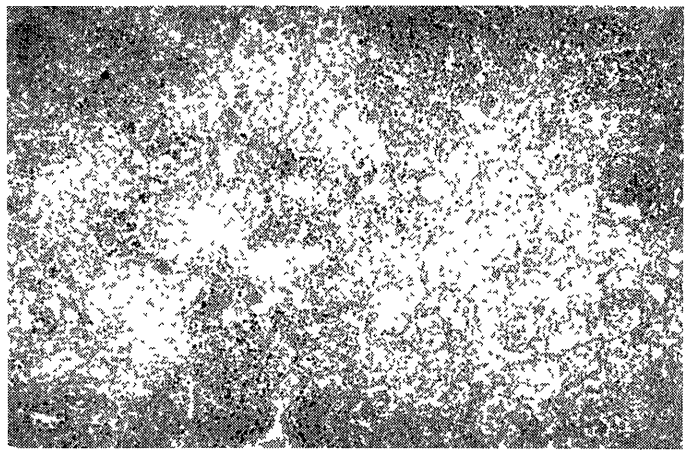

Fig. 3. Hemorrhagic interstitial pneumonia and Massive hemorrhage are found in alveolar spaces Mild to moderate edema and fibrosis of alveolar walls with moderate inflammatory cell infiltration are observed Hematoxylin and eosin stain, original magnification x 20

Report of Cases

Case 1 A 54-year-old Japanese man presented with cough, fever, headache, and hemoptysis Chest roentgenograms showed diffuse bilateral alveolar infiltrates Laboratory data showed blood urea nitrogen level of 172 2mg/dl (normal range, 8-20mg/dl), creatinine clearance level of 9 7mu/dl (normal range, 0 8-1 4mu/dl) At that time, the liver function tests revealed glutamic oxalacetic transaminase level of 1880mu/ml (normal range, 5-28mu/ml), glutamic pyruvic transaminase level of 1750mu/ml (normal range 0-24mu/ml), and leucine aminopeptidase level of 2430mu/ml (normal range, 235-440mu/ml) The patient died one week after admission The immediate cause of death was renal failure or exacerbation of respiratory failure An autopsy was performed 26 hours after death

Postmortem examination revealed major abnormalities in the lungs, kidneys, and liver The lungs were enlarged, relatively hardened and soiled Their surface were mottled with red and purplish hemorrhages On the cut surface there were edema, as well as red and brown areas of recent and old hemorrhages Light microscopically, there was massive hemorrhage in the alveolar spaces (Fig 3) There were areas of recent intra-alveolar hemorrhage and many gatherings of hemosiderin-laden macrophages (Fig 4) Diffuse fibrosis of the alveolar walls was prominent, and occasional small nodules of dense fibrous tissue were present Fibrinogen was present in alveolar spaces On gross examination the kidneys were soft and enlarged, and many foci of petechial hemorrhage were observed over the subcapsular surface and the cut surfaces Light microscopically, there were acute hemorrhage and thrombus formation in the glomeruli (Fig 5), and hemorrhagic cast formation in the collecting tubules (Fig 6)

Case 2 A 65-year-old Japanese man presented with cough, and pain of joint Chest roentgenograms showed

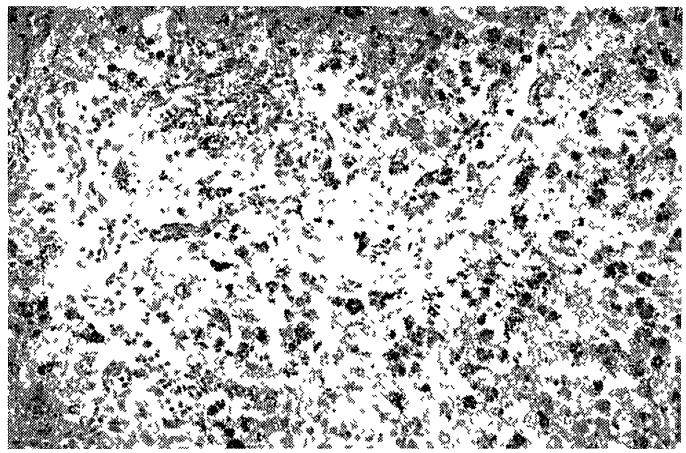

Fig. 4. There are extensive intra-alveolar hemorrhage and abundant hemosiderin-laden macrophages within alveoli Hematoxylin and eosin stain, original magnification x 100

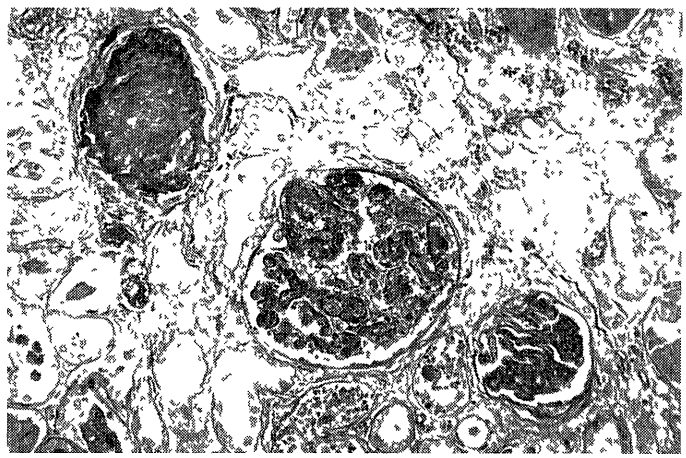

Fig. 5. Hemorrhage and thrombus formation are seen in the glomeruli Modified Mallory's stain for collagen, original magnification x 100

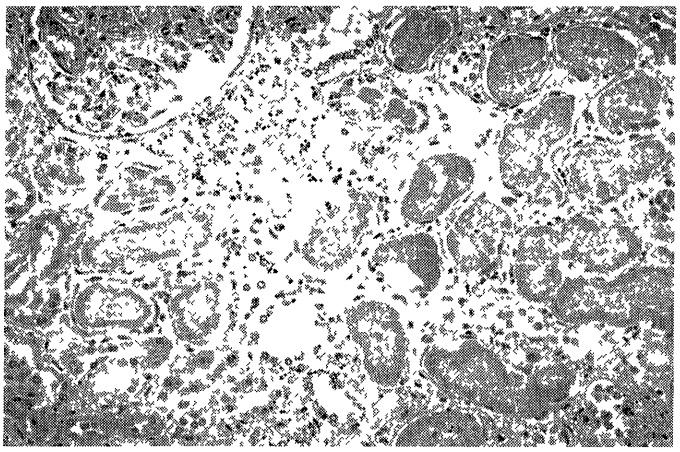

Fig. 6. Hemorrhagic cast formation and necrosis are detected in the tubules of Kidney Hematoxylin and eosin stain, original magnification x 100

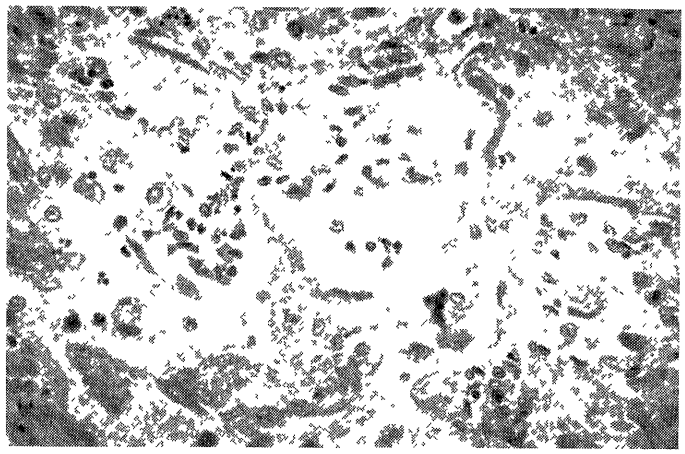

Fig. 7. Lung tissue demonstrating positive immunoperoxidase for linear deposits of IgG antibody on alveolar walls Immunoreaction for IgG x 400

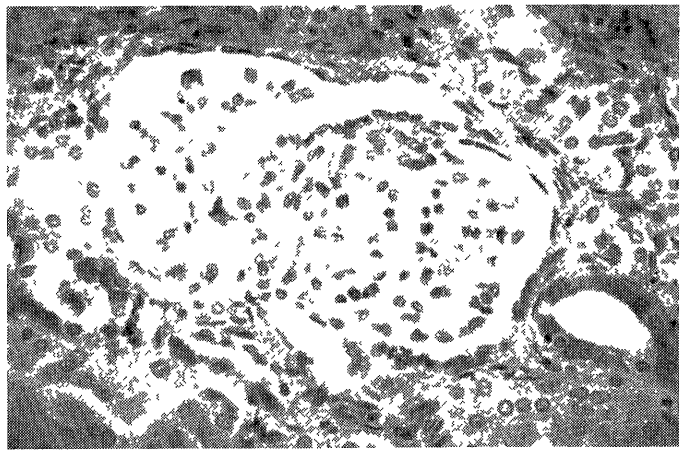

Fig. 8. Renal tissue revealing the linear immunoperoxidase staining for IgG antibody on Bowman's capsular basement membrane and tubules of kidneys Immunoreaction for IgG x 400

abnormal shadow in the left lung Laboratory data showed blood urea nitrogen level of 168mg/dl (normal range,8-20mg/dl) At that time, the liver function tests for glutamic oxalacetic transaminase level of 114mu/ml (normal range,5-28mu/ml), glutamic pyruvic transaminase level of 126mu/ml (normal range,0-24mu/ml), and leucine aminopeptidase level of 1076mu/ml (normal range,235-440 mu/ml) Gamma G globulin (IgG) titer was 1607 which was marker immunoglobulin of Goodpasture's syndrome On the other hand, other immunoglobulins were demonstrated such as IgA 304, IgG 89, and IgE 1210 The patient died ten days after admission The main cause of death was respiratory failure An autopsy was performed one hour thirty minutes after death

Postmortem examination revealed major abnormalities in the lungs, and in the kidneys On the cut surface of the lungs were edema, as well as red and brown areas of recent and old hemorrhages These lungs had acute and chronic pneumonia, fibrosis, emphysema and bulla formation Light microscopically, there was massive hemorrhage in the alveolar spaces There were areas of recent intraalveolar hemorrhage and many gatherings of hemosiderin-laden macrophages Diffuse fibrosis of alveolar walls was prominent Alveolar walls and intraalveolar fibrin-like materials were stained with anti-IgG (Fig 7) On gross examination the kidneys had fine granular nephrosclerosis Light microscopically, there were hemorrhagic cast formation and necrosis of renal tubles Extracapillary proliferative lesions showed circumferential cellular crescent associated with varying degrees of capillary tufts Glomerular capillaries, Bowman's capsular basement membrane and tubules of kidneys were stained by anti-IgG (Fig 8)

Discussion

In 1919, Goodpasture described the coexistence of pulmonary hemorrhage and glomerulonephritis 6 weeks after influenza in a young man (Goodpasture, 1919) The term Goodpasture's syndrome was coined by Stanton and Tange in 1958 to describe cases characterized by the coexistence of these manifestations (Saus *et al*, 1988) The autoantibodies were distributed along the alveolar septa basement membranes and the glomerular basement membranes in a linear manner, reflecting reactivity with specific glomerular basement membrane antigens The cause of the condition is unknown It has been suggested that it may be related to an autoimmune reaction The syndrome is now defined as an autoimmune disorder consisting of the triad of glomerulonephritis, lung hemorrhage, antibody against glomerular basement membrane antibody formation, and it includes a broad spectum of clinical features, resulting in injury to

tissues that is clinically manifeasted by acute glomerulonephritis (Beechler *et al.*, 1980; Beirne *et al.*, 1968; Goldstein *et al.*, 1986; Hogan *et al.*, 1978; Koffler *et al.*, 1969; Kondo *et al.*, 1986; Stugill and Zwestervelt, 1965). The present cases showed clinical and pathological features of rapidly progressive glomerulonephritis complicated with massive pulmonary hemorrhage. These evidences indicate the present cases to be a disease of the so-called Goodpasture's syndrome.

The mechanism underlying the association of progressive glomerulonephritis and alveolar hemorrhage in Goodpasture's syndrome has been clarified recently by the identification of antibody against glomerular basement membrane antibodies in glomerular and alveolar septa. In the past decade, many investigators have focused on the molecular origin and nature of the Goodpasture's antigen of renal glomerular basement membrane that binds the Goodpasture's antibodies. This information is of fundamental importance in delineating the molecular basis of the syndrome and in designing diagnostic tests. Basement membranes are complex extracellular structures containing at least four types of protein components. These include: (i) a collagen component, now referred to as type IV procollagen (Butkowski *et al.*, 1985, 1987; Saus *et al.*, 1988; Wieslander *et al.*, 1984, 1985); (ii) a glycoprotein component, now known as lamine (Beirne *et al.*, 1968; Ohno *et al.*, 1986; Timpl *et al.*, 1979); (iii) proteoglycans, which include heparan sulfate and chondroitin sulfate (Kanway and Farquhar, 1979; Kanway *et al.*, 1984); and (iv) entactin, a sulfated glycoprotein (Bender *et al.*, 1981). The mechanisms underlying the development of antibody against glomerular basement membrane antibodies remain to be studied.

Ramkin and Matthay (1982) proposed etiologies and immunopathogenic mechanisms of a group of systemic diseases which share pulmonary and renal abnormalities. They also discussed the following disease: (i) Goodpasture's syndrome; (ii) two connective tissue (collagen vascular) diseases, systemic lupus erytheromatosus and progressive systemic sclerosis (scleroderma); and (iii) three granulomatous vasculidities, Wegener's granulomatosis, lymphomatoid granulomatosis, and Churg-Strauss syndrome. Albelda and co-workers (1985) stated on diffuse pulmonary hemorrhage and presented a classification scheme depicted as a Venn diagram formed by four overlapping circles such as (1) pulmonary hemorrhage, (2) renal disease, (3) immune complex disease, and (4) antiglomerular basement membrane disease. This scheme results divided diffuse pulmonary hemorrhage into six categories (Group 1) pulmonary hemorrhage associated with glomerulonephritis and antiglomerular basement membrane antibody; (Group 2) pulmonary hemorrhage associated with renal disease without demonstrable immunologic abnormalities; (Group 3) pulmonary hemorrhage associated with glomerulonephritis and immune complex disease; (Group 4) pulmonary hemorrhage and immune complex disease without renal disease; (Group 5) pulmonary hemorrhege associated with antiglomerular basement membrane antibody without renal disease; (Group 6) pulmonary hemorrhage without demonstrable immunologic associations or renal disease. Categories 1, 2, and 3 groups contained diffuse pulmonary hemorrhage associated with renal disease and might be considered the generic term "Goodpasture's syndrome."

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