Massive Pulmonary Hemorrhage in Polyarteritis Nodosa (PN); Report of a Case

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We report a case of massive pulmonary hemorrhage which emerged in the course of polyarteritis nodosa (PN). Pulmonary hemorrhage was the major manifestation which determined the mortality of this patient, though severe renal failure concurrently developed. The diagnosis of PN should be considered in all cases of pulmonary hemorrhage coexisting with renal failure. As pulmonary hemorrhage can be life-threatening, early diagnosis is essential for the prompt start of adequate therapy.

Key words: Hemoptysis, Renal failure, Plasma exchange, Steroid pulse therapy, Cyclophosphamide

Although polyarteritis nodosa (PN) is a disease that can affect many organs of the body, massive pulmonary hemorrhage due to lung involvement is a rare manifestation (1, 2).

The diagnosis of PN is difficult in patients with hemoptysis and renal failure, because in addition to PN (1–6) several other disorders such as Goodpasture's syndrome, Wegener's granulomatosis (7–9), and systemic lupus erythematosus (10–11) more frequently cause pulmonary hemorrhage co-existent with rapidly progressing renal failure. Although immunosuppressive therapy is commonly used in all of these diseases, the treatments vary somewhat. As for the treatment of pulmonary hemorrhage in Goodpasture's syndrome, plasma exchange should be performed in addition to the administration of high dose steroid.

Pulmonary hemorrhage has recently been recognized as a significant contributory factor in the mortality of PN (12). Thus early diagnosis is essential for the prompt start of adequate therapy.

We encountered a case of PN with catastrophic pulmonary hemorrhage in association with rapidly progressing renal failure. Herein, we report our experience to emphasize the occurrence of massive pulmonary hemorrhage as a presenting symptom in PN.

CASE REPORT

A 66-year-old man, was admitted to Musashino Red Cross Hospital on September 1988 due to increasing shortness of breath and progressive deterioration of renal function. He had been treated as a patient with bronchial asthma, and had occasionally been given anti-inflammatory drugs for joint pain. He had no history of renal disease. About three weeks prior to admission, he began to feel weak in the lower limbs and became unable to get up from a low seat or a squatting position from one week before admission.

His body temperature was 36.8°C, blood pressure was 180/100 mmHg, pulse rate was 100/min, and respiratory rate was 26/min.

On examination he was markedly anemic and wide spread rales were heard on the right lung. Livedo reticulosa was present on both legs. There

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was no edema. The neurological examination revealed decreased knee and Achilles jerks.

The hematocrit was 19%, the white blood cell count was 14,700/mm³ with 87% neutrophils and 13% lymphocytes; no eosinophils were found. The platelet count was 15.9 x 10⁴/mm³. A specimen of arterial blood, drawn while he was breathing oxygen at 5 liters per minute via a face mask, revealed that the partial pressure of oxygen (PO₂) was 60.5 mmHg, the partial pressure of carbon dioxide (PCO₂) 20.9 mmHg, bicarbonate 11.6 mmol/l and pH 7.35. The serum sodium concentration was 129 mEq/l, chloride 102 mEq/l, K 6.8 mEq/l. Serum urea nitrogen (SUN) was 208.5 mg/dl, and serum creatinine (Cr) 14.1 mg/dl. Fasting plasma glucose concentration was 146 mg/dl. The erythrocyte sedimentation rate was 128 mm/h, CRP 22.9 mg/dl, and the RA factor 45.1 IU/ml. A quantitative test of immunoglobulins disclosed that IgG was 1,850 mg/dl, IgA 290 mg/dl, IgM 45 mg/dl, and IgE 846 U/l (normal range; <400 U/l). The serum complement factors C3, C4, and CH₅₀ were normal. The circulating immune complex was 4.0 µg/ml (normal range; <3.0 µg/ml). Tests for antinuclear antibodies were negative. And a test for anti-glomerular basement membrane (GBM) antibody was negative (This result was obtained 16 days later). Tests for HBs antigen and other anti-viral antibodies were negative. The prothrombin time, the partial thromboplastin time and other coagulation tests were normal. The urine had a specific gravity of 1.010, and gave a test for + glucose, 2 + protein; the sediment contained numerous red blood cells, 3 to 4 white blood cells per high-power field, and no casts. An electrocardiogram revealed sinus tachycardia and supraventricular extrasystole. An x-ray film of the chest (Fig. 1) revealed prominent infiltration in the right lung with a normal cardiovascular silhouette.

The patient was treated initially with hemodialysis, and packed red blood cell transfusion was done. Despite dialysis therapy no improvement of chest roentgenogram was noted, while hypoxemia improved slightly.

On the fourth hospital day, PO₂ abruptly fell with the development of massive hemoptysis. Intubation was performed and mechanical ventilation was started. Fiberoptic bronchoscopy revealed no endobronchial lesion but there was diffuse hemorrhage from all of the right bronchial divisions. At this time, Goodpasture's syndrome was considered to be the most probable diagnosis, and methylprednisolone pulse therapy combined with plasma exchange was performed. Although plasma exchange (51/day) was performed on three consecutive days, no improvement of PO₂ was observed, hemoptysis still continued, and infiltration on chest roentgenogram spread to the left lung. On the ninth hospital day, because this clinical course was considered atypical of Goodpasture's syndrome in terms of the poor response to plasma exchange, percutaneous needle renal biopsy was performed for the definite diagnosis. The biopsy specimen showed marked fibrinoid necrosis of interlobular and arcuate arteries with no granulomatous lesions, and no findings of crescentic glomerulonephritis. Immunofluorescence study showed no anti-GBM antibody deposition. At this time anti-GBM antibody was reported negative. These findings confirmed the diagnosis of polyarteritis nodosa, and subsequently cyclophosphamide (100 mg/day) was added to the treatment regimen on the 16th hospital day. However, the PO₂ continued to fall despite further elevation of the inspiratory oxygen concentration (Fig. 2), and he died of respiratory failure on the 19th hospital day.

Autopsy disclosed pulmonary hemorrhage. No
obvious source of bleeding was found in the tracheobronchial lesions. Light microscopy demonstrated diffuse intra-alveolar hemorrhage and hemosiderin-laden macrophages, and the fibrotic change of interalveolar septums was also found. There was no apparent signs of alveolar capillaritis, and arterioles and the larger pulmonary vessels were free of inflammation. Granulomas were not seen (Fig. 3).

Kidneys were atrophic, and brown in color. Sections through kidneys revealed indistinct corticomedullary junction, numerous infarcted areas, and thrombi in almost all larger vessels. Light microscopy disclosed that almost all arteries in the kidney, especially arcuate arteries were affected by the marked necrotizing vasculitis. In glomeruli, only ischemic changes were noted (Figs. 4, 5).

The other involved organs were spleen, pancreas, heart, liver, adrenal glands and gastrointestinal tract. Skin, muscles, peripheral nerves and brain were not examined in this case.

**DISCUSSION**

Massive pulmonary hemorrhage is an uncommon manifestation of PN. In Japan, only two cases have been reported (3, 4). In patients with hemoptyis and rapidly progressing renal failure, the differential diagnosis is difficult. As lung hemorrhage is rare in PN, the diagnosis of PN is often overlooked in favor of other diseases like Goodpasture’s syndrome or Wegener’s granulomatosis. However, Haworth et al (12) reported recently that pulmonary hemorrhage occurred in seven of thirty-six patients with microscopic polyarteritis causing serious morbidity. Thus, they emphasized the importance of the early recognition and treatment of pulmonary hemorrhage.

A therapeutic approach to the patients of PN with pulmonary hemorrhage has not been established and may well be different from that employed in Goodpasture’s syndrome. Therefore, the definite diagnosis of PN confirmed by histological examination may be essential. However, the histological findings of pulmonary hemorrhage in PN are often non-specific and vasculitis is usually not observed in the lung. Although Mark and Ramirez proposed diagnostic criteria for pulmonary capillaritis (13), it is often difficult to recognize, even for pathologists, and especially for those who are not experts in the pathology of non-neoplastic pulmonary diseases.

In fact, in this case no vasculitis was observed in the autopsy of the lung. The influence of O₂ toxicity, immunosuppressive therapy, and superimposed infection on the pulmonary lesions of PN may make the recognition of underlying capillaritis difficult in the autopsy material. Therefore, diagnosis should be made as soon as possible by
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Fig. 3. Histology of the left lung showing intra-alveolar hemorrhage and hemosiderin-laden macrophages. (HE staining; original magnification, ×400)

Fig. 4. Histology of the kidney showing marked fibrinoid necrosis of artery (left, original magnification, ×100) and glomeruli with slight ischemic change (right, original magnification, ×200). (PAS staining).

Fig. 5. Small arteries show marked intimal thickening and disruption of elastica lamina, and a portion of fibrinoid necrosis of the total wall. (elastica v. Gieson staining; original magnification, ×100).
renal biopsy as well as by renal angiography. As the initial diagnosis in this case was Goodpasture's syndrome, plasma exchange was added to high dose steroid treatment. But cyclophosphamide was started on the 10th hospital day, when the diagnosis of PN was finally established. This delay could be critical because the addition of cyclophosphamide is important if vasculitis is present.

The diagnosis of pulmonary hemorrhage is usually based on the clinical and roentgenographic manifestations, such as hemoptysis, infiltrates on the chest roentgenogram, anemia, dyspnea, and occasionally fever or chest pain, and most patients are too ill to tolerate an invasive study like transbronchial lung biopsy as in our case (14, 15). Other causes of pulmonary hemorrhage such as pulmonary edema due to advanced renal failure with volume overload, diffuse necrotizing infection (e.g., Aspergillus, Pseudomonas), pulmonary embolism, mitral stenosis, and severe coagulopathy, were excluded from the clinical setting and laboratory data.

The mechanism of pulmonary hemorrhage has previously been discussed extensively (15). Although apparent pulmonary capillaritis was not observed in this case, destruction of the alveolar wall including capillaries might be the cause of the hemorrhage. Derranged hemostasis, which is known to occur in uremia, may have contributed to the persistent pulmonary bleeding.

The treatment of choice in severe systemic vasculitis is combination therapy with corticosteroids and cyclophosphamide (16). Plasma exchange, added to the steroid pulse therapy, was shown to be effective in several previous reports in the literature (17–20), but the true efficacy remains undetermined. Terada et al (20) discussed in their report that plasma exchange might be effective for the patient with a high serum immune complex level. In contrast, our case showed only a slight elevation of the circulating immune complex level, which might account for the lack of response to the plasma exchange. Further studies are necessary to evaluate the efficacy of plasma exchange for PN.

In summary, a case of PN was described in which the major manifestations were massive pulmonary hemorrhage and renal failure. This case report suggests that pulmonary hemorrhage can be one of the important factors determining the prognosis of the patient with PN.

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REFERENCES


