The Seoul Journal of Medicine
Vol. 30, No. 3:195-201, September 1989

Massive Pulmonary Hemorrhage in a Patient with Systemic Lupus Erythematosus

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= Abstract =Pulmonary hemorrhage is a rare and often fatal manifestation of systemic lupus erythematosus (SLE) and enters the differential diagnosis of diffuse lung disease in patients with SLE. We have recently seen massive pulmonary hemorrhage in a 24 year old SLE patient with diffuse proliferative lupus nephritis. Pulmonary hemorrhage was diagnosed by the clinical triad of hemoptysis, anemia, infiltration on chest X-ray and by elevated carbon monoxide diffusing capacity (DLCO/VA).

Key words: ***SLE, Pulmonary hemorrhage, DLCO/VA***

INTRODUCTION

Pulmonary disease is one of the major complication of systemic lupus erythematosus (SLE) and occurs in as many as 50%-70% of patients during the course of their illness (Alarcon-Segovia *et al.* 1961; Estes *et al.* 1971). These include infection, pleurisy, interstitial fibrosis, diaphragmatic myopathy with consequent atelectasis, pulmonary edema and acute pneumonitis with or without pulmonary hemorrhage (Hunninghake 1979). However, massive pulmonary hemorrhage is a seldom appreciated aspect of the disease (Mintz *et al.* 1976).

We report one case to alert physicians to this rare but fatal complication of SLE.

CASE REPORT

A 24 year old woman was admitted to the Seoul National University Hospital with a 4 hour-history of hemoptysis, dyspnea and fever on the October 19th, 1988.

Received 1/7/89; revised 19/8/89; accepted 23/8/89

First admission

She was well until September 1987, when she was admitted to the hospital because of catatonic posture. Because she showed psychosis, persistent proteinuria, high anti-DNA antibody titer and positive fluorescent antinuclear antibody, she was diagnosed as SLE based on the revised diagnostic criteria for SLE by the American Rheumatism Association. Serum creatinine was 1.2 mg/dl, and 24 hour urine protein was 778 mg. The kidney biopsy showed diffuse increase of mesangial matrix associated with mesangial hypercellularity in light microscopy and abundant subendothelial, mesangial deposits in electron microscopy, so it was classified as diffuse proliferative lupus nephritis (Fig. 1, Fig. 2). Treatment with prednisolone 50 mg per day was begun and tapered to 17.5 mg per day with improvement for one year.

Second admission

One month prior to the second admission on October 17th 1988, she had easy fatigability, alopecia, decreased urine amount with 15 kg weight gain in spite of prednisolone therapy 60 mg/day for 4 weeks. On admission, the chest

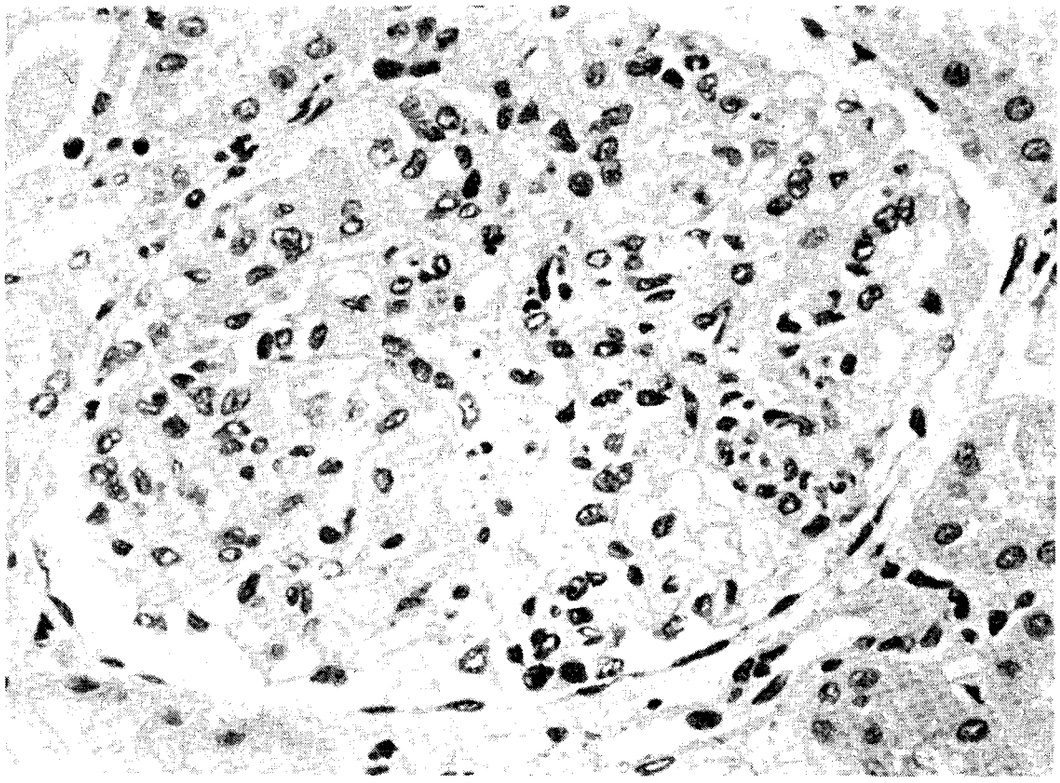

Fig. 1. Photomicrograph of the glomerulus. Diffuse increase of mesangial matrix associated with mesangial hypercellularity is demonstrated. Rather severe mesangial sclerosis is noted in portions. Peripheral capillary lumens are well opened with minor change of the wall. (H & E)

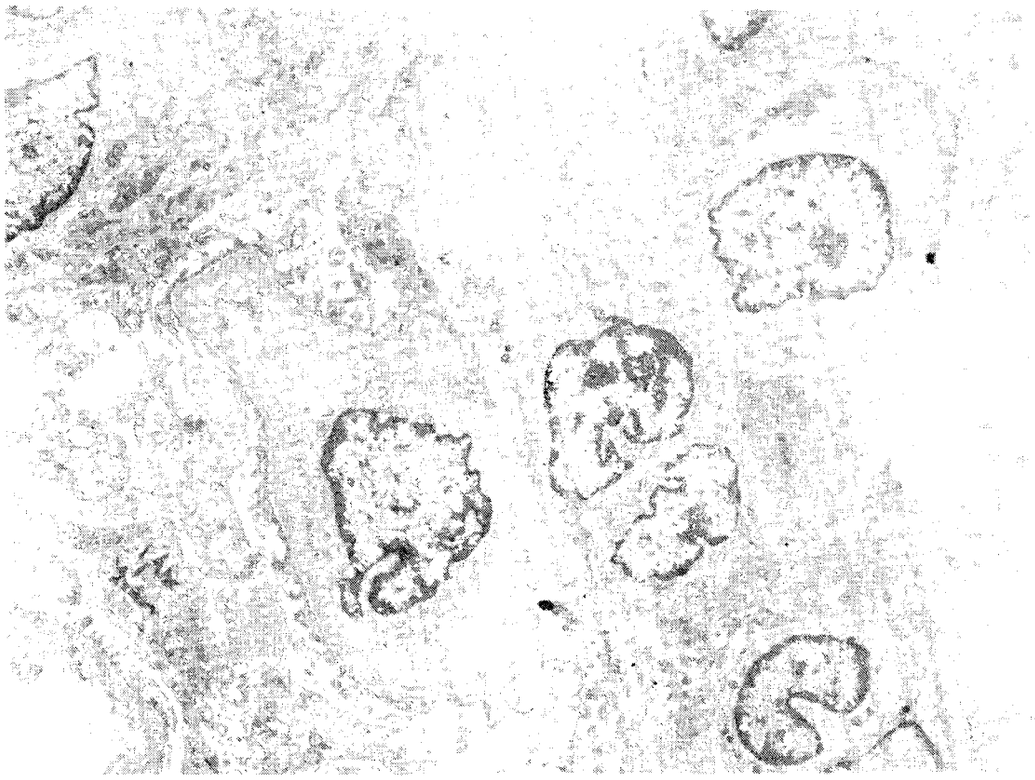

Fig. 2. Electron microscopic picture of the glomeruli, showing abundant subendothelial and mesangial deposits with areas of subepithelial deposits. Patchy effacement of foot process is seen.

roentgenogram was normal. The hemoglobin was 7.7 g/dl, hematocrit 23.6 %, the leukocyte count 7,000/mm^3 and platelet 170,000/mm^3. The coagulation profile was normal. The serum creatinine was 3.6 mg/dl, 24 hour urine protein was 2.76 g. The fluorescent antinuclear antibody (FANA) was positive with homogeneous type. Serum complement levels were C_3 35 mg/dl (normal, 45-105 mg/dl), C_4 12 mg/dl (normal, 15-45 mg/dl), and CH_{50} 10.2 u/ml (normal, 18-35 u/ml). The anti-ds DNA titer was 36 unit (normal, 0-25 unit). She was treated with ultrafiltration once and 10 mg nitrogen mustard twice (October 21st, 22nd). She was discharged with improvement on October 26th, 1988.

Third admission

In the evening of October 26th, she voided total gross hematuria with dysuria. In the morning of October 29th, she had fever, hemoptysis and dyspnea, and she was readmitted. On admission, the patient appeared to be acutely ill and was dyspneic. Her temperature was 39°C, respirations 28/min, heart rate 108/min, and blood pressure was 170/100 mmHg. Chest examination revealed bilateral rales especially on both middle lund fields. The chest roentgenogram (Fig. 4-A) showed alveolar infiltrates in both hilar areas and it was greatly increased 12 hours later (Fig. 4-B). Arterial blood gas values on room air showed pH 7.41, pCO_2 29 mmHg, pO_2 39 mmHg, HCO_3^- 19 mEq/l and with oxygen 5l/min via nasal prong, pH 7.42, pCO_2 31 mmHg, pO_2 96 mmHg, HCO_3^- 19 mEq/l. The hemoglobin was 5.4 g/dl, hematocrit 15.7 %, leukocyte 3500/mm^3, platelet 57,000/mm^3. The coagulation profile was PT 59%, aPTT 120 sec, bleeding time 5 min. The serum complement levels were C_3 11 mg/dl, C_4 26 mg/dl, CH_{50} 10.5 u/ml. Lupus anticoagulant was negative. Serum creatinine was 4.5 mg/dl, BUN 135 mg/dl, protein 4.4 g/dl and albumin 2.5 g/dl. Urinalysis was blood 3+, RBC numerous/HPF, WBC 10-20/HPF and granular cast 2-5/HPF. The patient was given methylprednisolone 1 g daily for 3 days from October 29th to October 31st under the impression of pulmonary hemorrhage and after that prednisolone 60 mg/day was continued. The patient was also placed with cefotaxime and amikin from October 29th. The daily hematocrit, transfusion amount and daily chest roentgenograms are given in Figure 3 and Figure 4. The hematuria became clear till November 1st and hemoptysis decreased and the chest roentgenogram (Fig. 4-C) improved. On the same day, the CO diffusing capacity corrected by alveolar volume (DLCO/VA) was 129.1%, at that time hemoglobin was 12.4 g/dl. Cough with hemoptysis increased from the evening of November 1st and she became irritable. The hematocrit level decreased to 30.1% from 35.9%. New infiltrates appeared in both upper lung fields in the chest roentgenogram (Fig. 4-D) and the DLCO/VA increased to 138.6% (Hb 10.3 g/dl). Arterial blood gas values were pH 7.34, pCO_2 33 mmHg, pO_2 44 mmHg, HCO_3^- 18 mEq/l with oxygen 6 l/min via nasal prong. The patient was intubated for mechanical ventilation. Large amounts of fresh blood gushed out from the endotracheal tube and the chest roentgenogram showed extensive consolidation (Fig. 4-E). The patient died in the early morning of November 3rd, 1988.

DISCUSSION

One of the salient clinical manifestations of this patient was the sudden development of diffuse pulmonary infiltrates, so the differential diagnoses in this patient were infection, congestive heart failure, uremia, drug reaction and lupus pneumonitis with or without pulmonary hemorrhage (Eagen *et al.* 1979; Churg *et al.* 1980) and often these factors may coexist. The common clinical features of pulmonary hemorrhage are hemoptysis, shortness of breath, cough, rales, severe hypoxemia usually accompanied by fever. In this patient, all of these features had been observed but begun with total gross hematuria and dysuria. It is possible that the cause of total hematuria may be the hemorrhagic complication of hyperheparinemia during nitrogen mustard treatment (Gilman *et al.* 1985). But that is less likely because of its delayed time onset. It is also possible that it was caused by the urinary bladder involvement of SLE. Alarcon-Segovia *et al.* (1984) reported that histologic changes of the urinary bladder were found in 16 of 35 necropsies from SLE patients. These included hemorrhage, interstitial cystitis, congestion, and vasculitis. And patients with histologic changes of the bladder were found to have more frequent pulmonary hemorrhage than those without. When this patient visited the hos-

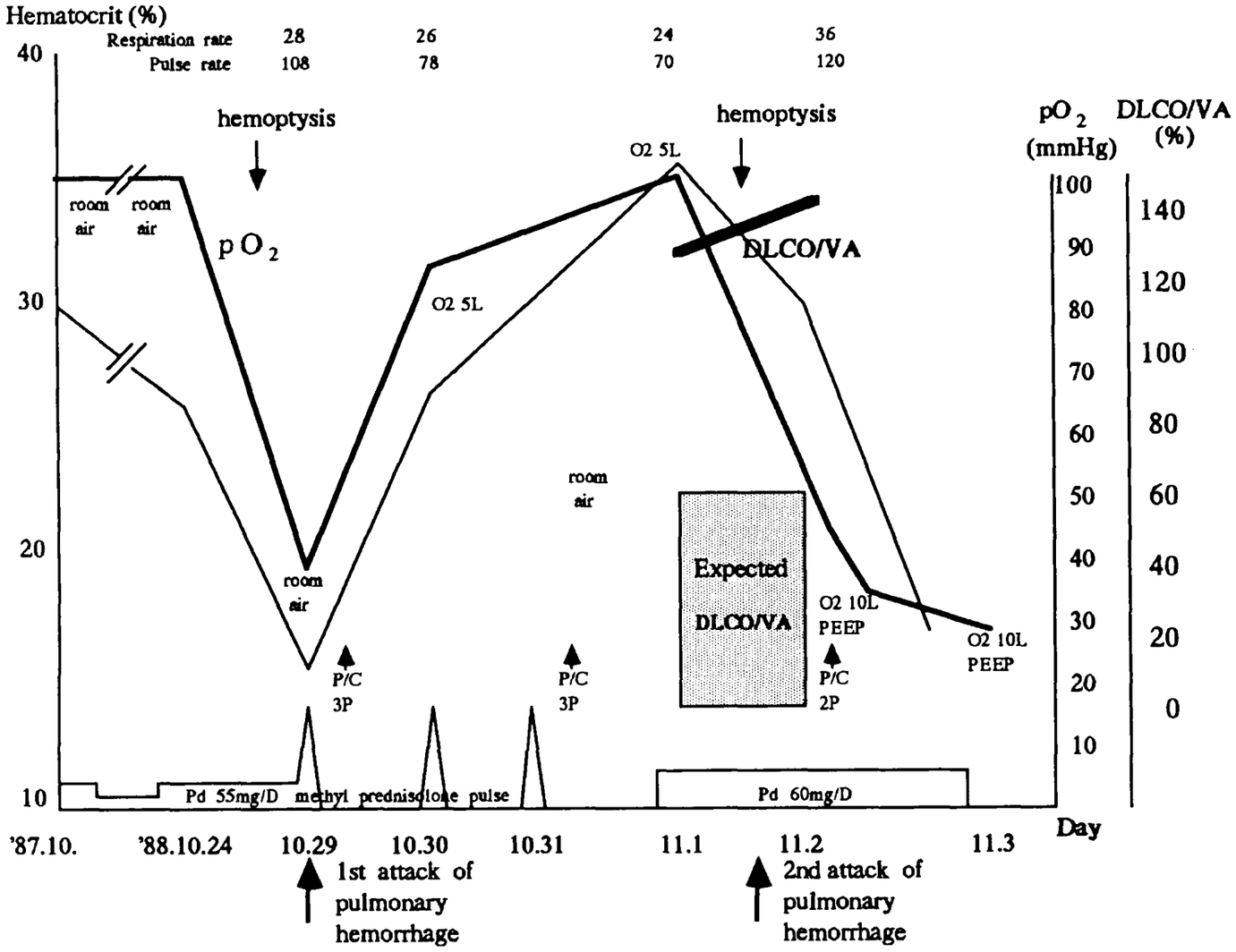

Fig. 3. Sequential changes of symptom, hematocrit with transfusion amount, pO_2, DLOC/VA and treatment during the two pulmonary hemorrhage attacks
P/C: packed red blood cells

pital on October 29th, pulmonary hemorrhage was suspected due to abrupt hemoptysis, decreased hematocrit, abnormal chest roentgenogram and severe hypoxemia. To rule out other diagnostic possibilities except pulmonary hemorrhage, we tested the carbon monoxide uptake expressed as DLCO/VA. DLCO/VA is a useful technique for detecting acute pulmonary hemorrhage (Ewan *et al.* 1976; Bowely *et al.* 1979; Rees 1984). Recent alveolar hemorrhage provides an extravascular pool of viable erythrocytes such that the amount of CO uptake is greater than predicted (Bowely *et al.* 1979). Rees (1984) has found the DLCO/VA to be more sensitive than the chest roentgenogram in detecting fresh alveolar hemorrhage. Ewan *et al.* (1976) examined serial changes in DLCO/VA in Goodpasture's disease and proposed that a 30% increase over the baseline value is highly suggestive of acute alveolar hemorrhage but a single value which is markedly elevated also seems to have diagnostic merit. As in this patient who had SLE and uremia, DLOC/VA is usually lower than the predicted value. In uncomplicated uremia, the mean baseline value is on the average 30 to 40% less than predicted (Lee and Streeton 1975) and average value of DLCO/VA of SLE patient was 66 % of the predicated value (Holgate *et al.* 1976). This is readily explained by histological fibrinoid change, necrosis and hyaline degeneration of interstitial tissues, alveolar walls and endothelial lining of the capillaries, all of which are frequently observed in the lungs of SLE patients (Koldes *et al.* 1946; Huang *et al.* 1965). In this patient, the DLCO/VA of November 1st was 129.1% which was markedly ele-

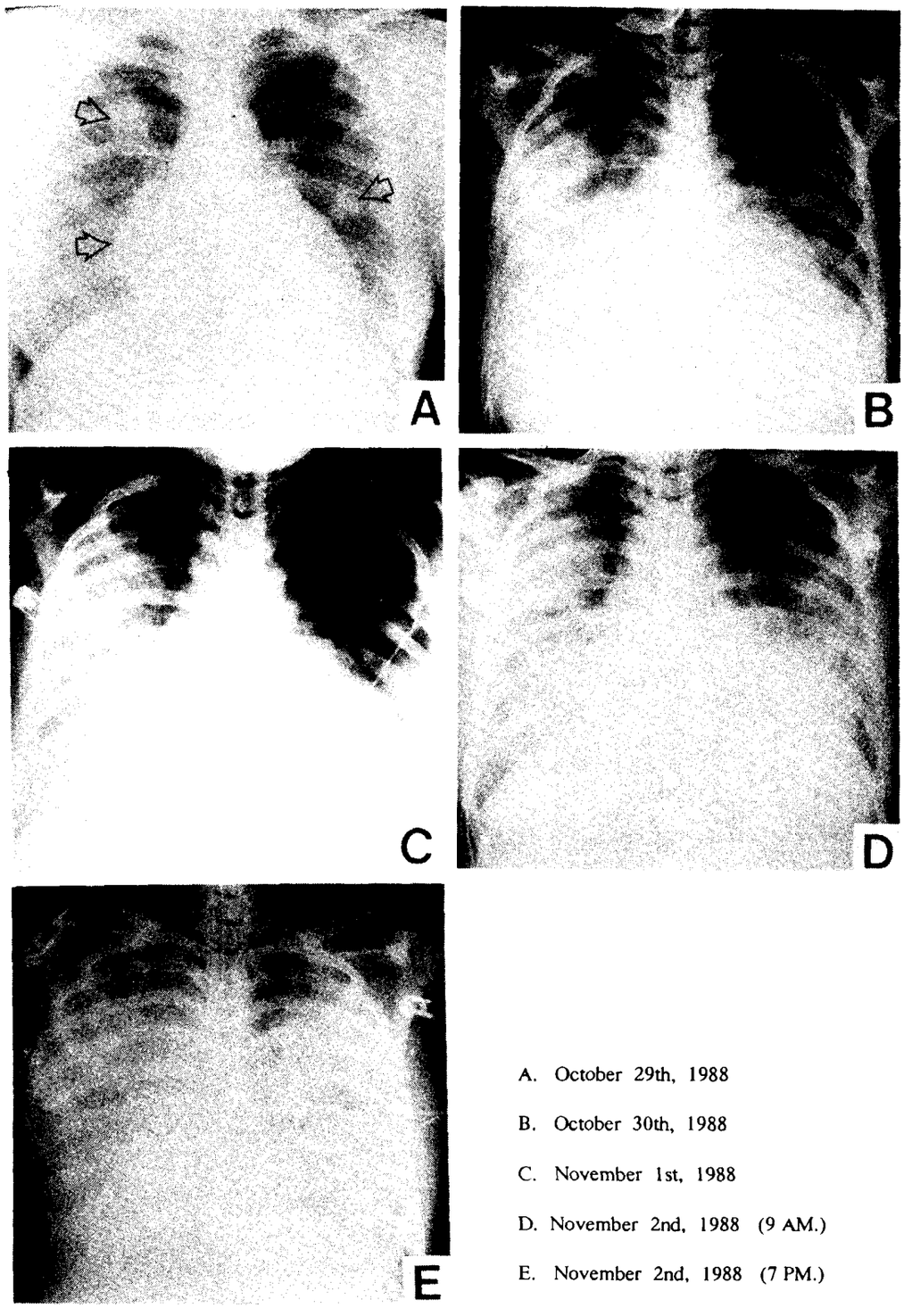

Fig. 4. Serial chest radiographs of the patient.

A. Initial chest radiograph showed ill-defined patchy air-space densities in right upper and both parahilar area (arrows). Cardiomegaly is seen.

B. Chest radiograph taken 12 hours after (A) showed diffuse bilateral air-space consolidation, especially in right side.

C. Chest radiograph taken 2 days after (B), following methylprednisolone pulse therapy, showed improved air-space consolidation especially in right lower and left upper lung fields.

D. Chest radiograph taken 1 day after (C), showed aggravated air-space consolidation in both upper lung fields as compared with (C).

E. Chest radiograph taken 10 hours after (D), 7 hours before death, showeu extensive air-space consolidation occupying the entire lungs.

vated in spite of azotemia (BUN 131 mg/dl, creatinine 4.5 mg/dl) and SLE. After three day's methylprednisolone pulse therapy, the first pulmonary hemorrhage began to decrease. Hemoptysis decreased, the hematocrit and pO_2 level were stable and a chest roentgenogram showed improvement on November 1st (Fig. 3, Fig. 4-C). When evidence of the second pulmonary hemorrhage such as increased hemoptysis, decreased hematocrit, hypoxemia and aggravated chest roentgenogram (Fig. 3, Fig. 4-D) appeared in the morning of November 2nd, the DLCO/VA increased further to 138.6% from 129.1% of November 1st.

The sequence of events responsible for massive pulmonary hemorrhage in SLE is not well defined. However its pathogenesis may be related to immune complex deposition, especially Ig G (Foldes 1946; Gould *et al* 1975; Churg *et al* 1980). These deposits were usually present in the alveolar septa, capillary loops and adjacent interstitium in the wall of small blood vessels and bronchioles in a granular pattern (Eagen *et al.* 1978; Myers *et al.* 1986). Electron dense deposits were observed at the alveolar capillary basement membrane by electron microscopy (Elliott *et al* 1970; Kuhn 1972; Gould and Soriano 1975; Katz *et al.* 1983).

Factors other than immune complex deposition may also play in precipitating diffuse alveolar damage and pulmonary hemorrhage. Twenty three cases of pulmonary hemorrhage in SLE have been reported in English written literature (Eagen *et al.* 1978; Carette *et al.* 1984; Leatherman *et al.* 1984). And factors which might precipitate pulmonary hemorrhage (e.g., infection, coagulopathy, uremia, volume overload and thrombocytopenia) were present in these cases. In this patient, although urine culture and blood culture were negative, it can not be ruled out that this patient had infection. And she had coagulopathy and uremia, so the pulmonary hemorrhage in this patient can be due to any or combination of these factors such as coagulopathy, uremia, thrombocytopenia, infection.

The prognosis of pulmonary hemorrhage of SLE patient is grave, and successful treatment is rarely feasible, even if treatment is initiated early. It is therefore important to suspect pulmonary hemorrhage even in the absence of hemoptysis in severely ill patients with bilateral pulmonary infiltrates and a sudden drop in hematocrit. We recommend that as soon as a presumptive diagnosis of pulmonary hemorrhage is reached, corticosteroid therapy should be started promptly and/or raised to high doses in pulse form with the simultaneous addition of cytotoxic agents.

REFERENCES

Alarcon-Segovia D, Alarcon DG. Pleuro-pulmonary manifestations of systemic lupus erythematosus. Dis. Chest. 1961, 39: 7-17

Alarcon-Segovia D, Abud-Mendoza C, Reyes-Gutierrez E, Iglesias-Gamarra A, Diaz-Jouanen E. Involvement of the urinary bladder in systemic lupus erythematosus. A pathologic study. J. Rheumatol. 1984, 11: 208-21

Bowley NB, Hughes JMB, Steiner RE. The chest X-ray in pulmonary capillary hemorrhage: Correlation with carbon monoxide uptake. Clin. Radiol. 1979, 30: 413-417

Carette S, Macher AM, Naussbaum A, Plotz PH. Severe, acute pulmonary disease in patients with SLE: Ten years of experience at the National Institutes of Health. Seminars in Arthritis and Rheumatism 1984, 14: 52-59

Churg A, Frankin W, Chan KL, Kopp E, Carrington GB. Pulmonary hemorrhage and immune complex deposition in the lung: Complications in a patient with systemic lupus erythematosus. Arch. Pathol. Lab. Med. 1980, 104: 388-391

Eagen JW, Memoli VA, Roberts JL, Mathew GR, Schwartz MM, Lewis EJ. Pulmonary hemorrhage in systemic lupus erythematosus. Medicine 1978, 57: 545-560

Eagen JW, Roberts JL, Schwartz MM, Lewis EJ. The composition of pulmonary immune deposits in systemic lupus erythematosus. Clin. Imm. Immunopath. 1979, 12: 204-219

Elliot ML, Kuhn C. Idiopathic hemosiderosis: Ultrastructural abnormalities in the capillary walls. Am. Rev. Resp. Dis. 1970, 102: 895-904

Estes D, Christian C. The natural history of systemic lupus erythematosus by prospective analysis. Medicine 1971, 50: 85-95

Ewan PW, Jones HA, Rhodes CG, Hughes JMB. Detection of intrapulmonary hemorrhage with carbon monoxide uptake. N. Engl. J. Med. 1976, 295: 1391-1396

Foldes J. Acute systemic lupus erythematosus. Am. J. Clin. Path. 1946, 16: 160-173

Gilman AG, Goodman LS, Rall TW, Murad F. Goodman and Gilman's The pharmacological basis of therapeutics. 7th edition, Macmillan publishing company, New York, 1985: pp. 1255

Gould DB, Soriano RZ. Acute alveolar hemorrhage in lupus erythematosus. Ann. Int. Med. 1975, 83: 836

Holgate ST, Glass DN, Haslam P, Maini RN, Turner--Warwick M. Respiratory involvement in systemic lupus erythematosus: A clinical and immunologic study. Clin. Exp. Immunol. 1976, 24: 385-395

Huang CT, Hennigar GR, Lyons HA. Pulmonary dysfunction in systemic lupus erythematosus. N. Engl. J. Med. 1965, 272: 288-293

Hunninghake GW, Fauci AS. State of the art. pulmonary involvement in the collagen vascular diseases. Am. Rev. Resp. Dis. 1979, 119: 471-503

Katz DA, Ben-Ezra J, Factor SM, Horoupian DS, Goldfischer S. Fatal pulmonary and cerebral fat embolism in systemic lupus erythematosus. JAMA. 1983, 250: 2666-2669

Kuhn C. Systemic lupus erythematosus in a patient with ultrastructural lesions of the pulmonary capillaries previously reported in the Review as due to idiopathic pulmonary hemosiderosis (letter). Am. Rev. Resp. Dis. 1972, 106: 931-932

Leatherman JW, Davies SF, Hoidal JR. Alveolar hemorrhage syndromes: Diffuse microvascular lung hemorrhage in immune and idiopathic disorders. Medicine 1984, 63: 343-361

Lee HY, Streeton TB. The lungs in renal failure. Thorax 1975, 30: 46-53

Mintz G, Galindo LF, Fernandez-Diez J, Jimenez FJ, Robles-Saaverda E, Enriquez-Casillas RD. Acute massive pulmonary hemorrhage in systemic lupus erythematosus. J. Rheumatol. 1978, 5: 39-50

Myers JL, Katezenstein AA. Microangiitis in lupus induced pulmonary hemorrhage. Am. J. Clin. Pathol. 1986, 85: 552-556

Rees AJ. Pulmonary injury caused by anti-basement membrane antibodies. Sem. Resp. Med. 1984, 5: 264

= 국문초록 =

전신성 홍반성 낭창 환자에서 관찰된 광범위한 폐출혈 1예

서울대학교 의과대학 내과학교실, 방사선과학교실*, 병리학교실**

김나영 · 김성권 · 송영욱 · 한성구 · 한진석 · 이정상 · 한용철 · 임정기* · 김용일**

전신성 홍반성 낭창 환자에서의 폐출혈은 매우 드물고 치명적인 임상상으로 이런 질환의 환자에서 흉부 X-선 사진상 전반적인 폐침윤이 나타날 때 반드시 감별 진단해야 할 임상상의 하나이다. 저자들은 최근 전신성 홍반성 낭창으로 치료받고 있던 24세의 여자환자에서, 폐출혈의 3대 임상적 소견인 혈담, 빈혈 및 흉부 X-선 사진상 폐침윤 양상과, 증가한 DLCO/VA로 진단된 폐출혈이, 매우 심하게 진행되면서 사망한 증례를 관찰하였기에 보고하는 바이다.