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**PULMONARY HEMORRHAGE SYNDROME AS A MANIFESTATION
OF DISSEMINATED INTRAVASCULAR COAGULATION:
ANALYSIS OF 10 CASES**

(Progress Report)

by

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In conducting the research described in this report,
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13. ABSTRACT Pulmonary hemorrhage occurred in seven patients with disseminated intravascular coagulation (DIC) and was produced in three monkeys when an experimental model for DIC was used. The principal manifestation of the syndrome was either the chief complaint for which patients entered the hospital, appeared with other coexisting complications of DIC, or occurred just prior to death. The onset of dyspnea, tachypnea, hemoptysis, rales, and a diffuse infiltrate by chest radiograph were usually interpreted as infectious processes; as a result therapy for DIC was withheld and the patients' conditions worsened. Pulmonary hemorrhage was the immediate cause of death in almost all patients.			

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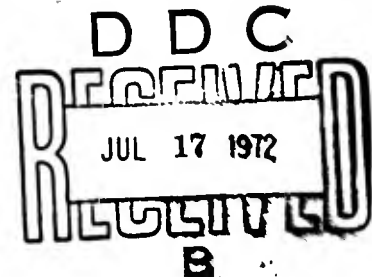
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ABSTRACT

PULMONARY HEMORRHAGE SYNDROME AS A MANIFESTATION OF DISSEMINATED INTRAVASCULAR COAGULATION: ANALYSIS OF 10 CASES

OBJECTIVE

To describe the hitherto unreported syndrome of pulmonary hemorrhage in disseminated intravascular coagulation (DIC).

METHODS

Six patients with pulmonary hemorrhage and DIC were examined at the Massachusetts General Hospital, Boston. The case history from a seventh patient at the Hadassah University Medical Center, Jerusalem, Israel, was also reviewed. The syndrome of pulmonary hemorrhage was reproduced in three monkeys when each was challenged with hemolytic IgG derived from the plasma of a donor alloimmunized with red blood cells.

RESULTS

All ten subjects developed pulmonary hemorrhage together with the coagulation changes of DIC. Because the clinical signs of onset of dyspnea, tachypnea, hemoptysis, rales, and a diffuse infiltrate by chest radiograph were initially misinterpreted as infectious processes, therapy for DIC was withheld and the patients' conditions worsened. Pulmonary hemorrhage was the immediate cause of death in almost all patients.

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INTRODUCTION

During an analysis of organ dysfunction in 45 cases of disseminated intravascular coagulation (DIC) (1), a syndrome with pulmonary hemorrhage was repeatedly observed. Clinically, it consisted of the sudden onset of dyspnea, tachypnea, hemoptysis, rales, and a diffuse infiltrate on chest radiogram. Necropsy revealed extensive pulmonary hemorrhage and edema. This report presents the findings in six patients (1), in one reported case that we were permitted to review (2), and in three out of five monkeys where the syndrome was reproduced when an experimental model (3) for DIC was used.

CASE REPORTS

The clinical data for the 10 subjects is presented in Table 1 and the coagulation data in Table 2. All patients experienced bleeding from multiple sites (petechiae, purpura, wounds, venipuncture sites) during DIC. Heparin (calculated in U.S.P. units) was always given intravenously every 4 hours. The monkeys were not treated. In no case was tumor or bronchopneumonia observed in the lungs at autopsy, nor were there signs of congestive heart failure, coronary, or other forms of heart disease.

Case 1 (#16¹): A 50-year-old man with acute promyelocytic leukemia had two episodes of DIC while in the hospital. Both were associated with administration of 6-mercaptopurine and one was treated successfully with heparin. On the 24th hospital day the bone marrow aspirate was found to be packed with promyelocytes; therefore cytosine arabinoside therapy was initiated. Two days later a dry cough appeared, the temperature rose to 104°F, a preexisting small hematoma enlarged markedly, and coagulation changes of DIC occurred (Table 2). Severe chest pain, bilateral pleuritic rubs, and, several hours later, wheezing and hemoptysis appeared. The respiratory rate rose from 20 to 30 and the pulse from 90 to 120; the blood pressure remained stable. Shortly thereafter wheezes were heard throughout the entire right chest while breath sounds diminished. He died 3 hours after onset of chest pain. Autopsy revealed extensive pulmonary hemorrhage and edema, but no leukemic infiltrates.

Case 2 (#27¹): A 55-year-old woman entered the hospital with acute myelomonocytic leukemia. Examination revealed basilar rales and an initial chest radiogram disclosed an infiltrate in the right lower lung field. Therapy with 6-mercaptopurine was begun. During the ensuing several days the infiltrate enlarged to involve predominately the right middle lobe; the respiratory rate rose from 20 to 40 and the patient was obviously worse. By the fifth day, diffuse inspiratory rales were present, and follow-up radiographs disclosed an extensive bilateral butterfly

Table 1

Clinical Data

Case (Ref)	Age Sex	Etiology DIC	Dyspnea	Chest pain	Pleural friction rub	Rales Hemoptysis	X-ray	Misc	Respiration (rate/min)	Blood pressure	Autopsy Lung weight	Pulmonary hemorrhage causing death
1 (16 ¹)	50 M	acute promyelocytic leukemia; CA	+	+	+	+	ND	cough wheezing	20 + 30	stable	+ 1200g	yes
2 (27 ¹)	55 F	acute myelomonocytic leukemia; CA & 6MP	+	+	+	+	butterfly pattern		20 + 40	stable	ND	yes
3 (24 ¹)	68 M	prostatic adenocarcinoma		+		+	diffuse		24 + 32	stable	alive	
4 (12 ¹)	61 M	prostatic adenocarcinoma; 32p*	+				"edema"		20 + 60	S-60 D-40	+ 1300g	yes
5 (21 ¹)	33 M	acute promyelocytic leukemia; CA & 6MP				+	ND		20 + 28	stable	+ 2000g	no
6 (29 ¹)	46 F	acute myelomonocytic leukemia; CA & 6MP				+	diffuse		20 + 25	S-60 D-40	ND	yes
7 (2 ²)	37 M	acute promyelocytic leukemia	+			+	ND	cough			+	yes
8 (139 ³)	Monkey	experimental	+			+	ND	EKG, giant P waves	25 + 60	stable	+	yes
9 (63 ³)	Monkey	experimental					ND		32 + 60	M-55	+	yes
10 (172 ³)	Monkey	experimental					ND		20 + 41	M-35	+	?

CA = cytosine arabinoside

6MP = 6-mercaptopurine

*24 hours after testosterone and ³²p were given, the acid phosphatase rose from 0.7 to 8.5 Sigma units

+ = present or done

ND = not done

S = systolic blood pressure
D = diastolic blood pressure
M = mean blood pressure
θ = normal combined weight of human lungs 600g

Table 2

Coagulation Data

Test	Normal	Patients		Monkeys	
		During pulmonary hemorrhage (N=7)	Changes during onset of hemorrhage (N=4)	During pulmonary hemorrhage (N=3)	Changes during onset of hemorrhage (N=3)
Hematocrit (volume %)	37-50	29	+ 12 (N=4)	16	+ 22
Platelet count (per ml)	250,000 ± 50,000	24,000	+ 130,000 (N=3)	116,000	+ 240,000
Prothrombin time (sec)	11.5 ± 1.0	18	+ 5 (N=4)	18	+ 7
Fibrinogen (mg/100 ml)	230 ± 35	113	+ 280 (N=2)	138	+ 144
Fi titer*	≤ 1:8	1:74			
Euglobulin clot lysis time (min)	> 120	3/5 abnormal			

* Fi titer of fibrin(ogen) degradation products.

infiltrate that spared the apices and bases. On the seventh day she developed marked respiratory distress, right lateral pleuritic pain and hemoptysis. During an 8-hour period the pain localized to a small area where a friction rub was heard. Examination of the bloody sputum revealed no organisms. Subsequently the pulmonary symptoms worsened; the hematocrit fell to 24%, petechiae, purpura, bleeding from venipuncture sites, and coagulation changes of DIC appeared. The respiratory rate remained at 40 and the blood pressure stable at normal levels. Heparin therapy (6,400 units) was instituted. Although the coagulation tests improved slightly and the rales decreased, the respiratory distress persisted and she died. Autopsy was not performed.

Case 3 (#24¹): A 68-year-old man with prostatic adenocarcinoma metastatic throughout the pelvis entered the hospital because of hemoptysis. During the previous evening generalized pain had appeared in the right chest. At admission myocardial ischemia was suspected for which demerol was given immediately. Within minutes a massive hematoma appeared at the injection site in the deltoid muscle. Examination also revealed decreased breath sounds and rales in the right base. The respiratory rate was 24. DIC was diagnosed and heparin therapy (12,500 units initially, then 9,400 units) was begun. During the next 2 days the hematomas enlarged, the hematocrit fell from 40 to 28 and the respiratory rate rose to 32; the blood pressure was stable. A chest radiogram revealed small opacifications throughout the lungs. By the third day all of the coagulation tests listed in Table 2 (except the platelet count) had returned toward normal, although severe bleeding persisted clinically and the lung infiltrates were unchanged. Hemoptysis recurred and on the next day the chest radiogram disclosed increased infiltration in the right base. During the sixth hospital day new hematomas were still forming. Extensive rales were present bilaterally and a chest radiogram revealed large infiltrates in both bases. On the seventh day the bleeding stopped, the hematomas resolved, the pulmonary findings disappeared, and all coagulation tests returned to normal. Heparin therapy was discontinued, and the patient was discharged from the hospital. He is well 2 years later.

Case 8 (monkey #139): A healthy female *Macaca irus* monkey was challenged by intravenous infusion of 150 hemolytic units of IgG derived from the plasma of a donor alloimmunized with red cells* (3). Within 30 minutes of infusion, the respiratory rate rose from 25 to 60 and severe respiratory distress was evident. The hematocrit fell from 38 to 18%, while the blood pressure remained stable. Before the animal died, 1 hour after infusion, the findings of DIC and renal failure were present. The respiratory distress was severe and bloody nasal froth was observed. A continuous electrocardiogram disclosed the appearance of giant P waves, followed

*A hemolytic unit is defined as the amount of IgG necessary to produce 50% hemolysis in an *in vitro* test system containing 3% red cells in saline and complement. The experimental model used in these animals was modified to allow the use of purified hemolytic IgG instead of whole plasma (3).

by asystole. Autopsy revealed numerous pulmonary hemorrhages (Fig. 1). Microscopically, multiple fibrin thrombi were also present in small arterial and venous vessels (Fig. 2).



Fig. 1. Diffuse pulmonary hemorrhage (H+E x 190).



Fig. 2. Multiple fibrin thrombi in pulmonary vasculature (H+E x 200).

DISCUSSION

Pulmonary hemorrhage, the immediate cause of death in almost all of the subjects in this series, is a frequent manifestation of DIC (14%) and is rarely recognized during life. These cases illustrate that pulmonary hemorrhage may be the chief complaint for which a patient is hospitalized; it may precede other clinical and coagulation signs of DIC, may occur as one of several coexisting complications of DIC, or may be the harbinger as well as direct cause of death. Regardless of the time when the syndrome occurred during the hospital course, its significance in these cases and others in the literature (4) was rarely appreciated immediately. Dyspnea, tachypnea, rales, and an infiltrate by chest radiograph were usually interpreted as representing infectious processes. This was true even when DIC was already documented. During the time consumed in search for infection, therapy for DIC was withheld and the patients' conditions worsened. In only one case (#3) were DIC and pulmonary hemorrhage recognized at an early stage; in this case large doses of heparin were given and despite the presence of widespread tumor, the patient improved and has been well for 2 years. Since pulmonary hemorrhage is a serious complication, and often a fatal sequel of DIC, recognition and prompt institution of therapy are important.

The mechanism by which pulmonary hemorrhage occurs is unknown, although it may be similar to the course of events in the "hemorrhagic shock syndrome." There, pulmonary hemorrhage follows after blood loss has resulted in systemic hypotension. Direct observation of the pulmonary microvasculature has disclosed that vasoconstriction occurs in the distal arterioles, resulting in rupture of the capillaries that arise just proximally and thereby causes pulmonary hemorrhage (5,6). Recently, Veith et al (5) have shown that many types of insults other than exsanguination and shock elicit pulmonary hemorrhage. Examples include homologous blood transfusions or even exposure of blood to foreign (nonendothelialized) surfaces of a pump-oxygenator machine. Preliminary experimental studies in animals have suggested that pulmonary hemorrhage may occur when DIC is induced by the intravenous infusion of thrombin, but is blocked when heparin is administered simultaneously (7). It is possible that fibrin thrombi formed during DIC and trapped by the pulmonary microvasculature may also accentuate the process of pulmonary hemorrhage (8).

LITERATURE CITED

1. Colman, R. W., S. J. Robboy, and J. D. Minna. Disseminated intravascular coagulation: an approach. *Amer. J. Med.*, in press (Feb 72).
2. Polliack, A. Acute promyelocytic leukemia with disseminated intravascular coagulation. *Amer. J. Clin. Path.* 56: 155-161, 1971.
3. Lopas, H., N. I. Birndorf, and S. J. Robboy. Experimental transfusion reactions and disseminated intravascular coagulation produced by incompatible plasma in monkeys. *Transfusion*, 11: 196-204, 1971.

4. Hand, J. J., D. C. Kent, and V. N. Hook. Meningococcal meningitis and meningococcemia associated with pulmonary infiltrates and hemoptysis. *Dis. Chest*, 54: 552-554, 1968.
5. Veith, F. J., J. W. C. Hagstrom, A. Panossian, et al. Pulmonary microcirculatory response to shock, transfusion, and pump-oxygenator procedures: A unified mechanism underlying pulmonary damage. *Surgery*, 64: 95-109, 1968.
6. Wilson, J. W., N. B. Ratliff, and D. B. Hackel. The lung in hemorrhagic shock. I. *In vivo* observations of pulmonary microcirculation in cats. *Amer. J. Path.* 58: 337-352, 1970.
7. Huber, G., R. Mason, C. Pegg, et al. Production, reversal, and prevention of experimental hyaline membrane disease following disseminated intravascular coagulation. *Clin. Res.* 17: 415, 1969.
3. Blaisdell, F. W., R. C. Lim, and R. J. Stallone. The mechanism of pulmonary damage following traumatic shock. *Surg. Gynec. Obstet.* 130: 15-22, 1970.