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Acute Respiratory Failure Due to 2′ Deoxycoformycin*

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Abstract. 2′ Deoxycoformycin is a new chemotherapeutic agent with promising application in lymphoblastic leukemias. Previous Phase I trials have not indicated potential for pulmonary toxicity. We wish to report a case of respiratory failure presenting with sudden onset of severe hypoxia, tachypnea, and rapid evolution of diffuse alveolar infiltrates and pleural effusions. Aggressive management with high level positive end-expiratory pressure (PEEP) and steroids achieved a successful outcome.

Key words: Respiratory failure – Chemotherapy – Lymphoblastic leukemia – Pulmonary toxicity

Introduction

2′ Deoxycoformycin (2′ Dcf) is a tight-binding inhibitor of the intracellular enzyme adenosine deaminase. It has been shown to exert a specific anti-T-lymphocyte activity, producing an immune incompetent state like that seen in severe combined immune deficiency, where inborn absence of adenosine deaminase has been documented [1]. Because leukemic T-cell populations are highly sensitive to 2′ Dcf, it represents a new specific therapy for adult and childhood lymphoblastic leukemias. Animal studies and published current Phase I trials have indicated only lymphopenia and uric acid nephropathy as specific organ toxicity [2]. We wish to report a case of overwhelming respiratory failure caused by 2′ Dcf which responded rapidly to aggressive respiratory support and steroid therapy.

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Case Report

A 9-year-old black male weighing 33.3 kg with a history of acute lymphoblastic leukemia, null-cell type, was admitted in January 1980 for further chemotherapy. In April 1978 his first course of chemotherapy consisted of vincristine, prednisone, L-asparaginase, intrathecal methotrexate and cranial irradiation (2400 rads) followed by maintenance with 6-mercatopurine, methotrexate, vincristine and prednisone, and he achieved a remission lasting until October 1979. Thereafter, he remained in relapse despite treatment with doxorubicin, vincristine, prednisone and cyclophosphamide. On 19 December 1979 he received 2′ Dcf 0.25 mg/kg by single IV push for three successive days which induced a transient depression of lymphoblasts in the bone marrow. A mild conjunctivitis was noted on the 4th day after chemotherapy, which resolved in two days. A second course of 2′ Dcf, 0.25 mg/kg for five successive days, was begun 2 January 1980. The patient experienced anorexia, nausea and fever to 38.4 °C on the 2nd day of chemotherapy, and vomited on the 2nd and 5th days. On the 5th day a mild decrease in his urine output and fever to 40 °C occurred. Blood, throat, and urine cultures were negative and the chest film was unremarkable (Fig. 1). Hemoglobin was 11.3 g/dl, leukocyte count 1,700 (differential of 80% neutrophils, 2% bands, 1% eosinophils, 1% basophils, 8% monocytes, 3% lymphocytes, 1% atypical lymphocytes, 1% nucleated red cells); platelet count 157,000. Uric acid was 10.0 mg/dl; however, uric acid crystals were seen in the urine. He was begun on antibiotic coverage (cephazolin, gentamicin, carbenicillin) and allopurinol 300 mg/day. Urine output increased with intravenous hydration, and urine pH greater than 6.5 was maintained. He continued to have daily temperature spikes to 39 °C, and intravenous trimethroprim-

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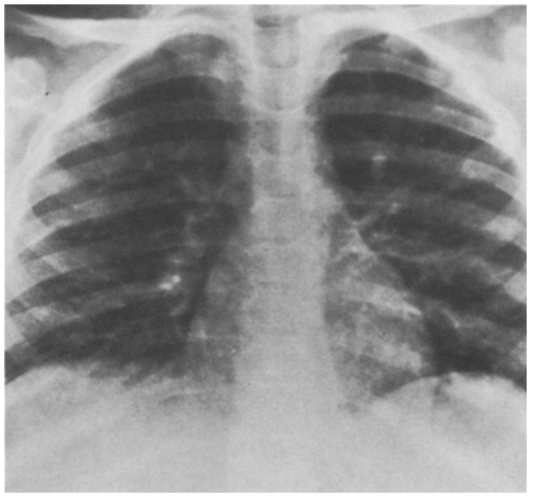

Fig. 1. Chest X-ray on 5th day of chemotherapy

sulfamethoxazole (20 mg/kg trimethoprim) was added. On 19 January he experienced increasing respiratory distress, and, while sitting up, was observed to have a brief generalized seizure with loss of consciousness lasting 2 min. His weight had increased to 34.1 kg, but he had no peripheral edema and fluid balance had been stable. Lumbar-puncture yielded clear colorless spinal fluid with normal opening pressure; protein 18 mg/dl, glucose 80 mg/dl, 1 monocyte; gram stain, culture and cytology were negative. On physical examination breath sounds were markedly decreased at both lung bases. Chest X-ray revealed large bilateral confluent alveolar infiltrates and pleural effusions. On FiO_2 0.4 arterial pH was 7.50, pCO_2 25, pO_2 51, O_2 sat 89%.

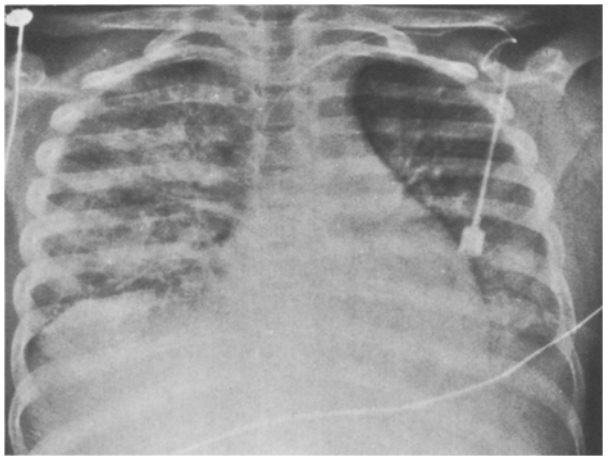

Fig. 2. Chest X-ray after onset of severe respiratory failure (after thoracentesis)

Bilateral thoracentesis was performed, draining 400 ml clear straw-coloured fluid from the left hemithorax and 200 ml from the right, negative for cytology and culture. A transient clinical improvement followed and arterial pO_2 rose to 83 torr (FiO_2 0.4), but he remained tachycardic at 180–210 beats/min, and tachypneic (40–60 breaths/min); within one hour arterial pO_2 again fell to 41 torr. Chest X-ray confirmed extensive bilateral alveolar infiltrates without residual pleural effusions (Fig. 2). He was then transferrred to the Intensive Care Unit.

On admission to the Intensive Care Unit he was awake, afebrile, with circumoral and nail bed pallor. Respiratory rate was 48/min, heart rate 180/min, blood pressure 100/60 torr. Diffuse coarse rales were present bilaterally. Intubation was immediately followed by expulsion of copious, frothy, straw-coloured sputum. On FiO_2 0.7, 5 cm PEEP arterial blood gas was: pH 7.42, pCO_2 44, pO_2 41, O_2 sat 95%; serum Na^+ 139, K^+ 3.0, Cl^- 98, CO_2 27, BUN 4, creatinine 0.6, glucose 162, ionized calcium 1.88 mEq/L, lactate 4.7 mEq/L. A pulmonary artery catheter was placed; central venous pressure was 9 torr, pulmonary artery pressure 36/18 torr, mean pulmonary capillary wedge pressure 20 torr. Furosemide 20 mg was administered intravenously and wedge pressure decreased to 12 torr. Subsequent respiratory management and hemodynamic variables are outlined in Table 1.

Cultures of blood, urine, and sputum were negative for bacterial pathogens; sputum Gram-Weigert stain for *Pneumocystis carinii* and cytology were negative, as were serum titers for viral and fungal pathogens. Sputum colloid osmotic pressure (COP) was 18.3 torr, compared to blood COP of 16.2 torr. Sixteen hours after intubation, arterial blood gases were still markedly abnormal on FiO_2 0.5, and 32 cm PEEP (Table 1). Sputum COP was 16.0 torr, blood COP 15.7 torr. Methylprednisolone 3 mg/kg/day was begun. Eighteen hours later, oxygenation had improved and sputum production was minimal. A dramatic clearing of the chest film occurred by the 3rd day of support (Fig. 3) and the patient was weaned from the ventilator over the next 48 h.

Antibiotics were discontinued during this time, with the exception of trimetheprim-sulfamethoxazole during weaning from steroids. He was discharged to the floor with no respiratory symptoms and no renal dysfunction 6 days after admission to the Intensive Care Unit. Viral convalescent titers were negative. On 21 January, because of bone marrow relapse, M-AMSA 100 mg/m^2/day was given until 25 January. While pancytopenic he developed *Candida albicans* sepsis and died on 8 February. At autopsy, the lungs showed fungal pneumonia with diffuse

Table 1. Summary of respiratory management and hemodynamic data

Respiratory settings					Arterial blood gases					Hemodynamic data				
Date	Time	IMV (br/min)	PEEP (cm H_2O)	FiO_2	pH	pCO_2 (mmHg)	pO_2 (mmHg)	O_2 sat %	CI (l/min/m^2)	HR (b/min)	BP (mmHg)	$\overline{PAP}$[a]	WP[a]	Comment
1/9	11.20 am (admission)	12	5	0.7	7.42	44	41	75	3.0	180	100/60	26	20	Serum lactate 4.71 mEq/I Furosemide 20 mg IV given
1/9	4.04 pm	8	24	0.7	7.41	46	59	90	3.0	190	100/50	24	12	
1/10	4 pm	2	32	0.5	7.46	46	64	92	4.4	182	120/64	20	4	Serum lactate 1.02 mEq/I Methylprednisolone 3 mg/kg IV begun
1/11	3 pm	2	34	0.4	7.44	39	69	94	4.6	142	136/76	26	11	
1/11	10 pm	2	32	0.4	7.46	41	95	97	4.6	130	112/70	13	2	
1/12	11 am	2	23	0.4	7.48	35	90	97	–	128	118/62	25	10	
1/13	9 am	0	7	0.4	7.45	34	100	98	–	90	130/66	10	5	
1/14	9 am		T-tube	0.35	7.48	31	75	96	3.6	82	126/84	8	1	

IMV = intermittent mandatory ventilation; PEEP = positive end-expiratory pressure; CI = cardiac index; HR = heart rate; BP = systemic blood pressure; $\overline{PAP}$ = mean pulmonary artery pressure; WP = pulmonary capillary wedge pressure

[a] Corrected for mean intrapleural pressure, monitored continuously by intraesophageal balloon

hemorrhage and consolidation. There was no evidence of fibrosis, hyaline membrane formation, or pleural adhesions.

Discussion

This patient presented with fever and rapid pleuropulmonic reaction at the conclusion of a course of 2′ Dcf. Although no eosinophilia in the peripheral differential blood count was noted, a finding strongly suggestive of drug-induced pulmonary hypersensitivity reactions, it should be considered that bone marrow suppression is very rapid after 2′ Dcf. We also felt it was too dangerous to perform bronchoscopy or biopsy to document eosinophilic lung infiltration, because of the necessity for high PEEP to maintain oxygenation. Nevertheless, the sudden appearance of infiltrates, effusions and copious protein-rich sputum, and the rapid improvement after initiation of steroid therapy favor the hypothesis that an acute hypersensitivity reaction had taken place.

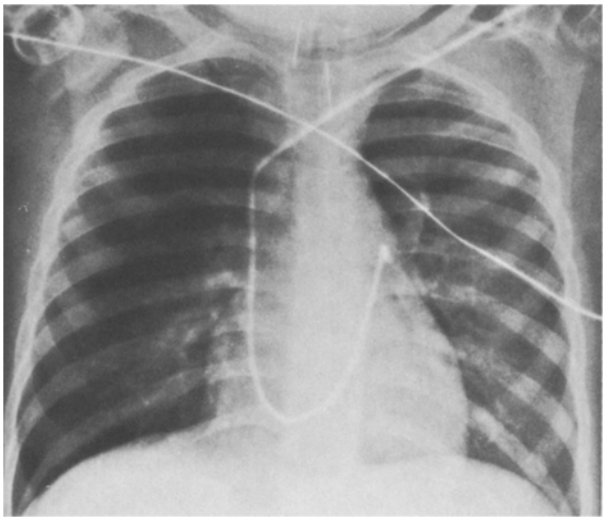

Fig. 3. Chest X-ray on the third day of mechanical ventilation (see text)

The clinical presentation and roentgenographic appearance were uncharacteristic of *Pneumocystis carinii* pneumonia. Gram-Weigert stain can be negative in active *P. carinii* pneumonia, but one could have expected to recover the organism in this case, since alveolar fluid production was overwhelming.

Bacterial pneumonitis is also a potential cause of rapidly developing pulmonary infiltrates. However, gram-stain and sputum cultures were consistently negative. Furthermore, complete resolution of a severe gram-negative pneumonia in four days would be extremely unlikely in an immunosuppressed patient. Viral pneumonia may present with fulminant respiratory failure and has been responsive to steroids and dehydration [3]. Infiltrates may be interstitial or confluent, as in this patient. However, we failed to document seroconversion for viral antigens even after recovery of immune competence.

This patient had received a total dose of 180 mg doxorubicin. This low dose does not obviate the possibility of cardiogenic pulmonary edema, especially since occult cardiac failure may become severe with the onset of sepsis. Indeed the initial high wedge pressure and marked tachycardia would support this suspicion. However, the patient had been hypoxic for several hours; inability to meet metabolic oxygen requirements was documented by a significant lactic acidosis. Thus, we feel this initial poor cardiac function was not responsible for the onset of pulmonary failure, but reflected deterioration of left ventricular function consequent on prolonged hypoxia, which improved with return of adequate oxygenation. As may be seen in Table 1, cardiac output was well-maintained without inotropic support even when high PEEP was applied, and wedge pressure remained normal after stroke volume improved. In addition, the high protein content of the sputum implicates a non-cardiogenic etiology [4].

In conclusion we believe that 2′ Dcf adds one more drug to the list of potential causes of hypersensitivity-induced respiratory failure [5]. Prompt, aggressive treatment rapidly reversed the disease in our patient without apparent residual parenchymal damage. High doses of steroids were instrumental in a rapid and complete recovery.

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