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Three Cases of Interstitial Pneumonia Occurred in Children with Chemotherapy for Acute Lymphoblastic Leukemia

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Abstract

We report three cases of acute interstitial pneumonia which occurred in children with anti-leukemic chemotherapy. Sudden onsets of dyspnea were their presenting symptoms. Chest X-rays showed ground-glass appearance. All of them had been diagnosed as acute lymphoblastic leukemia 17, 20 and 28 months prior to development of diffuse interstitial lung disease. Of the 2 patients studied for chest CT, both had bilateral diffuse ground-glass opacities. None of the patients was positive on blood culture for bacteria or fungi and had serological evidence of recent infection of cytomegalovirus or Epstein-Barr virus. Clinical and radiologic improvement promptly followed by 2 to 6 days of steroid therapy. Steroids were maintained for 12, 16 and 24 days in each patients until there was no clinical deterioration. Most of the laboratory findings were normal at discharge and on their subsequent follow-up at the outpatient clinic. Because of the extreme severity of the respiratory distress at the time of diagnosis, many kind of drugs were tried, and bronchoalveolar lavage had not been performed. The causes of these cases remain unknown. However, possibility of alveolar or interstitial cell damage by chemotherapeutic agents per se, or inflammatory cytokine activation triggered by unrecognized infection might be implicated in the pathogenesis. All of the three patients underwent following chemotherapy uneventfully and survived.

Key Words: Interstitial pneumonia, Leukemia, Chemotherapy, Children

Introduction

Interstitial lung diseases (ILDs) or diffuse infiltrative lung diseases represent a heterogeneous group of lung disorders of known or unknown cause, generally characterized by dyspnea, diffuse parenchymal lung infiltrates, and impaired gas exchange. The most common type of ILD is idiopathic interstitial pneumonia (IIP). Although the clinician and the pathologist all have different points of view, IIP has been classified into 5 categories[1,2] : 1. UIP=usual interstitial pneumonia, 2. DIP=desquamative interstitial pneumonia, 3. NSIP=nonspecific interstitial pneumonia (=GIP, giant cell interstitial pneumonia), 4. BOOP=bronchiolitis obliterans organizing pneumonia 5. AIP=acute interstitial pneumonia (=DAD, diffuse alveolar damage, =LIP, lymphocytic interstitial pneumonia). ILDs usually affects middle-aged and older persons. To our knowledge, it is very rare in children.

Another category of idiopathic pneumonia syndrome (IPS) describes a clinical entity of diffuse lung injury that occurs after marrow transplantation[3] or chemotherapeutic drugs, such as cytarabine,[4] and for which no infectious cause can be identified. Possible causes of IPS after marrow transplantation include chemoradiation damage, unrecognized infection, injury from intravascular inflammation (e.g., endotoxemia), and graft-vs-host disease (GVHD) associated with cytokine activation.[3]

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Case Report

Case 1

On Jul. 7, 1998, a 5-year-old boy developed sudden dyspnea after 3 days of cough. He was diagnosed as acute lymphoblastic leukemia (ALL) in Feb. 1996 and

under a maintenance chemotherapy. For the last 2 weeks he had been received 180 mg of Cytarabine, 200 mg of Cyclophosphamide weekly and 40 mg of 6-TG daily for 2 weeks. On exam, his temperature was 37.8℃, BP 110/80, pulse rate 148/min, respiratory rate 78/min. His face was pale, lips and fingers were cyanotic. Arterial blood gases (ABG) showed pO_2; 32 mmHg, pCO_2; 25.4 mmHg, pH; 7.52, HCO_3; 20.5 mmol/L, BE; -0.8, O_2 saturation; 74.4%. These findings were compatible with respiratory alkalosis.

The lungs were clear initially, but rales were noticed from 2nd day. Chest X-ray (CXR) and conventional computed tomographic (CT) scan showed diffuse ground-glass opacity in both lung fields (Fig. 1, 2). Serum levels of BUN, creatinine and electrolyte were normal. Serum level of total protein was low and s-GOT/GPT, s-LDH levels were increased. Level of s-GOT return to normal most rapidly 1 week later. Blood culture for bacteria and fungi was negative. Antibodies to mycoplasma, cytomegalovirus(CMV) and Epstein-Barr virus (EBV) were negative except EBV-VCA IgG (Table 1).

Treatment with Bactrim (TMP/SMX) and oxygen was started soon after admission. The next day, dexamethasone in dose of 10 mg/m^2/day was tried because he had more severe hypoxia and hypocapnea (pO_2; 29.8 mmHg, pCO_2; 27.6 mmHg, pH; 7.54, HCO_3; 23.8 mmol/L, BE; 3.7, O_2 saturation; 66.5%.). On 3rd day, his

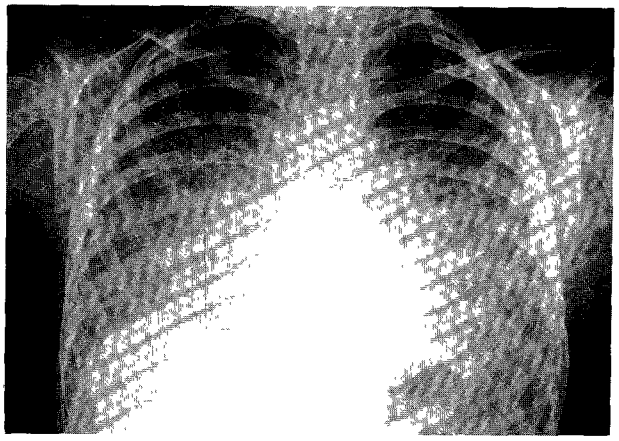

Fig. 1. Chest X-ray of case 1 showing bilateral diffuse ground-glass opacity.

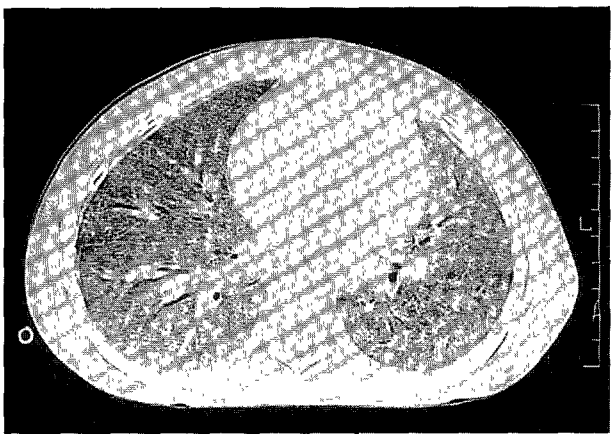

Fig. 2. Chest CT scan of case 1 showing bilateral ground-glass opacity.

symptoms and CXR findings worsened, and antiviral agent (Ribavirin) and antibiotics (Klaricid) were added to the medication. He began to improve in dyspnea and CXR showed objective decrease in diffuse opacity from 6th day (after 4 days of steroid treatment) and could take a liquid meals from 9th day. He was weaned off the oxygen on 11th day. The steroids were kept on use for 14 days on admission and 10 days at the outpatient clinic.

Case 2

On Jul. 10, 1998, a 12-year-old girl was admitted because of sudden dyspnea with 1 day of fever, cough and lethargia. Since Jan. 29, 1997, she had been received antitumor chemotherapy for ALL for 17 months. Three and two weeks ago (Jun. 19 and Jun. 26 in 1998), she had been examined at OPD and received 1.5 mg of Vincristine, 200 mg of Cytarabine and Dexamethasone tablets on each visit. One week prior to admission, she received 17 mg of Methotrexate and 62.5 mg of 6MP for 7 days.

Her temperature, BP, pulse and respiration were 37.8℃, 110/70, 128/min. and 56/min. respectively. ABG showed pO_2; 37.9 mmHg, pCO_2; 38.2 mmHg, pH; 7.43, HCO_3; 23.8 mmol/L, BE; -0.1, O_2 saturation; 72.2%. The lungs were clear. Both CXR and a high resolution CT

Table 1. Drugs received prior to symptoms and clinical profiles in three patients.

		Case 1 (5 yr/M)	Case 2 (12 yr/F)	Case 3 (11 yr/M)
Drug used for 2 weeks prior to symptoms		CPM*, Ara-C†, 6TG‡	VCR§, Ara-C Dexa‖, MTX¶, 6MP**	CPM, Ara-C, 6TG
Recent use of G-CSF/Blood		(-)	(-)	(-)
Chief complaints		Dyspnea	Dyspnea	Dyspnea
PE	Respiration (/min)	78	56	46
	Auscultation	Rales at 2nd day	Breath sound ↓	Rale (-)
	Others	Cyanosis		Alae nose flaring
Lab	Peripheral WBC(/μℓ)	16,300	9,800	1,000
	P/B/L/M (%)	81/0/14/4	96/1/3/0	54/3/38/5
	Total lymphocyte (/μℓ)	2,282	294	380
	Hemoglobin (g/dL)	11.3	11.1	10.7
	Platelet (/μℓ)	570,000	581,000	324,000
	CRP (mg/dl)	2.2	19.9	5.1
	Anti-mycoplasma HI	neg	neg	neg
	Bacteria/fungi culture	neg	neg	neg
	Total pro/alb (g/dL)	4.9/3.6	5.4/3.5	5.7/3.7
	GOT/GPT (IU/L)	460/202	24/45	41/7
	LDH (IU/L)	2,688	568	1,890
	pO_2(mmHg)	32	37	70 (on O2 3L/m)
	pCO_2(mmHg)	25	38	29
	CMV IgM/IgG	(-/-)	(-/+)	(-/-)
	EBV-VCA IgM/IgG	(-/+)	(-/+)	not done
	Tsubset T4/T8 (%)	not done	64.8/21.3	27.1/18.6
	NKcell/NKactivity(%)	not done	5.3/22.1	10.6/49.2
	Chest X-ray	Ground glass	Ground glass	Ground glass
	Chest CT	Ground glass	Ground glass,ILST††	not done
Tx	O2 supplement (day)	11	4 (3d+DC‡‡+1d)	11
	Steroid used (day)	24	12 (6d+DC+6d)	16 (3d+DC+13d)
	Drug used long-term	Bactrim, Ribavirin	Bactrim, Ribavirin	Bactrim, Acyclovir
Time to clear CXR§§ opacity after steroids (day)		4	3 (1st trial) 2 (2nd trial)	3 (1st trial) 6 (2nd trial)

CPM*: cyclophosphamide, Ara-C†: cytosine arabinoside, 6TG‡: 6-thioguanine,
VCR§: vincristine, Dexa‖: dexametasone, MTX¶: methotrexate, 6MP**: 6-mercaptopurine,
ILST††: interlobular septal thickening, DC‡‡: discontinue, CXR§§: chest X-ray

(HRCT) scan of chest showed diffuse ground glass opacity in both lung fields. Interlobular septal thickening was also seen in HRCT (Fig. 3, 4). Other laboratory findings were presented on follwing table (Table 1).

Antibiotics (Amocla, Cefotaxime), Bactrim, Dexamethasone, Ribavirin had been initiated the day of admission, her condition and CXR findings had improved considerably on 2nd hospital day. On 3rd day, she was weaned off the oxygen while steroids were tapered, and discharged from hospital on 6th day without steroid medication. Three days later (Jul. 18, 98), she was readmitted with dyspnea, with pO_2 and oxygen saturation on room air dropped to 36.4 mmHg and 71.7%, respectively. A repeat CXR showed aggrevated interstitial infiltrates. O_2 inhalation with intravenous steroids (Solucortef 125mg followed by Dexamethasone 3mg tid) was administered, and 2 days later she was asymptomatic with improved CXR findings (Fig. 3).

Case 3

On Jan. 31, 1999, a 11-year-old boy was admitted because of sudden onset of dyspnea and fever. He had been underwent antitumor chemotherapy for ALL for the last 20 months. For the last 2 weeks, he had been received 400 mg of Cytarabine and 400 mg of

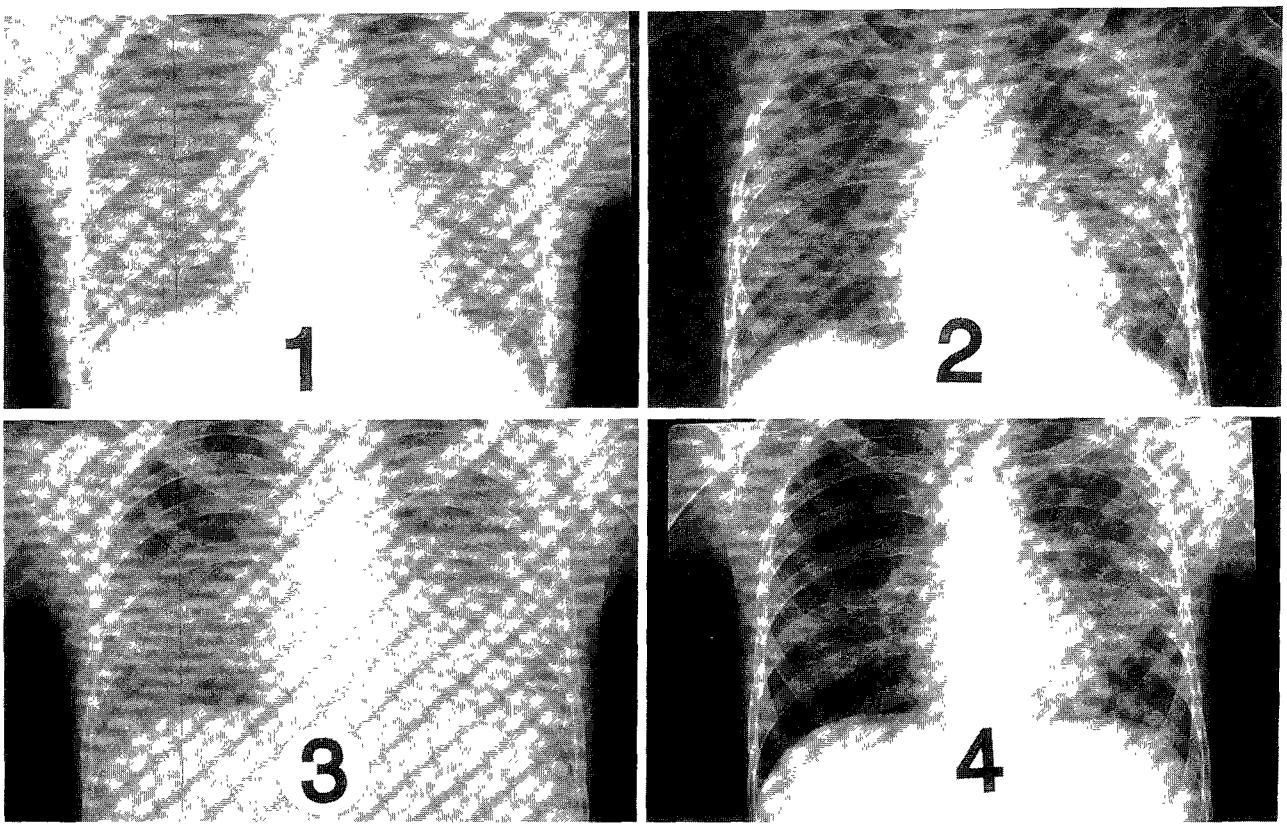

Fig. 3. Chest X-ray finding of case 2. (1): Bilateral ground-glass opacity on admission. (2): Improved finding with 3 days of solu-cortef & dexamethasone. (3): Worsened 3 days later from stopping. (4): Improved again after resuming steroid for 2 days.

Cyclophosphamide weekly, and 80 mg of 6-TG daily. Her temperature was 38.0℃ and other vital signs were as following. BP; 130/70, pulse; 120/min, respiration; 46/min. ABG during O_2 inhalation 3L/min by nasal cannula showed pO2; 70.8 mmHg, pCO_2; 29.7 mmHg, pH; 7.41, HCO_3; 18.5 mmol/L, BE; -5, O2 saturation; 95%. Other laboratory findings were presented in the table. The lungs were clear. CXR showed diffuse ground-glass opacity in both lung fields (Fig. 5).

As his condition was very poor, he had been treated with several antibiotics (Vancomycin, Ceftazidime, Clindamycin, Klaricid, Bactrim), Acyclovir, Solucortef and Dexamethasone from the day of admission. His symptoms and diffuse opacity in CXR improved remarkably on 3rd day. He was kept on oxygen, but weaned off steroid thereafter. On 7th day, however, Dexamethasone 2.5mg qid was resumed as dyspnea became more severe. CXR on 8th day showed recurrent diffuse opacity. On 12th day, he weaned off oxygen supplement. On 14th day (Feb. 13, 1999), he was discharged with 5 days of oral steroid medication as his CXR finding were grossly normal (Fig. 5).

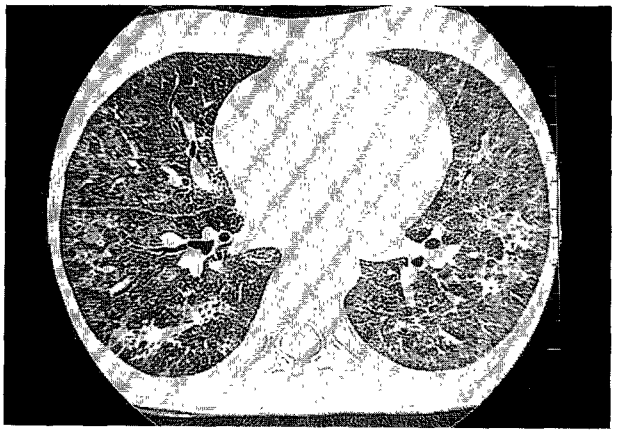

Fig. 4. High resolutional CT scan of case 2 showing bilateral ground-glass opacity with interlobular septal thickening.

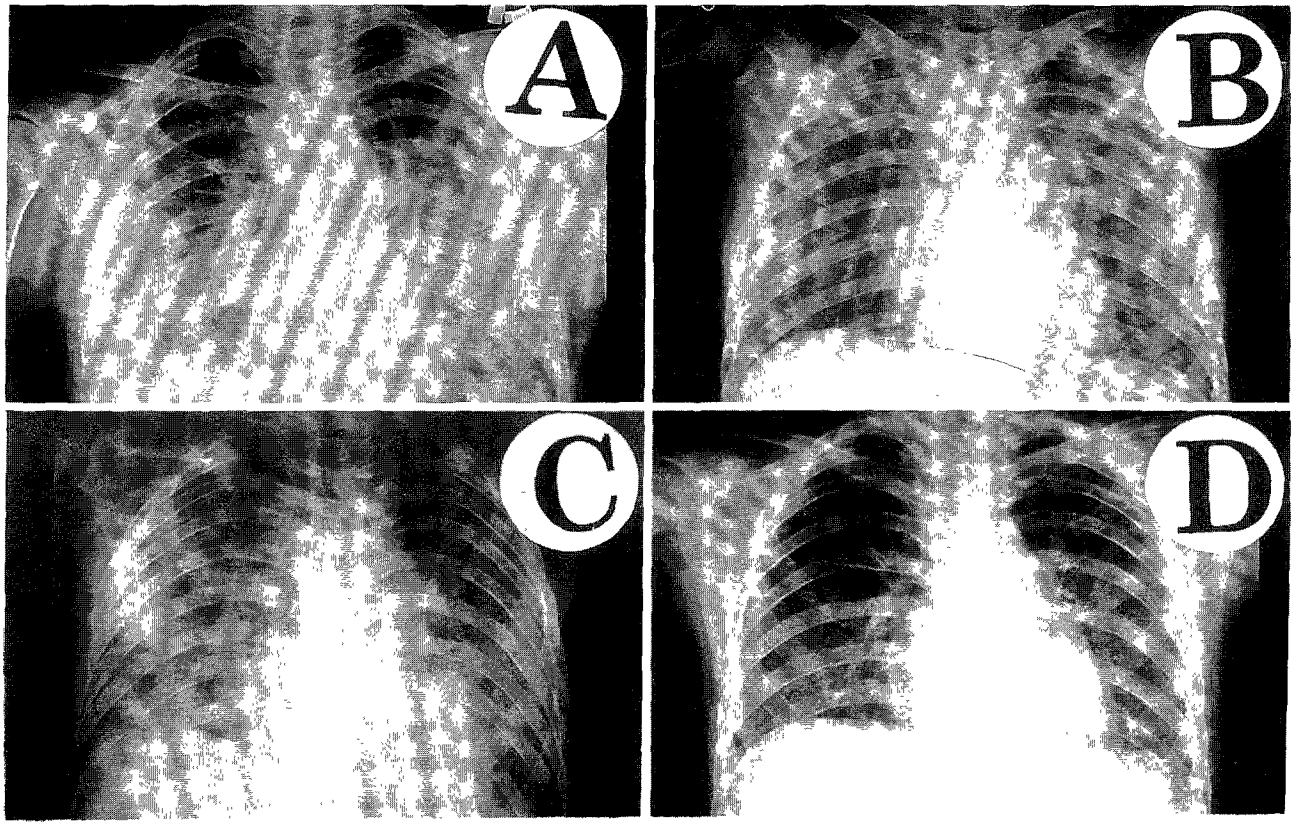

Fig. 5. Chest X-ray finding of case 3. A: Bilateral diffuse ground-glass opacity on admission. B: Improved finding after 3 days of dexamethasone treatment. C: Worsened afer 5 days from weaning. D: Grossly normal finding with 6 day dexamthasone

Discussion

Although idiopathic interstitial pneumonia (IIP) is likely to be multifactorial in terms of clinical risk factors, transient activation of inflammatory cytokines in the lungs during the recovery period from the toxicity of drugs may be implicated in the pathogenesis.[5] CD4+ cells were not counted in our cases, but total peripheral lymphocyte counts were greater than 200 cells/mm^3. Of two patients who tested for T cell subset, one patient showed high CD4+ lymphocyte ratio(Table 1). A central role has been proposed for both macrophage-derived cytokines (TNF-α, IL-1, IL-6) and lymphocyte-derived cytokines (interferon-γ, IL-2) in mediating the manifestations of GVHD.[3]

The patients had severe dyspnea and could not tolerate any of diagnostic procedure. Although bronchoalveolar lavage (BAL) is generally considered to be a safe procedure, it cannot be performed in severely dyspneic or hypoxic children. Both *Pneumocystis carinii* (*P. carinii*) and CMV can produce ground-glass opacity and CMV typically produces nodules, masses, or dense consolidation with extrathoracic evidence of CMV disease. Although possibility of *P. carinii* and other unrecognized infectious origin arise, *P. carinii* is unlikely to be the cause of this diffuse lung disease. The radiologic findings seen in our patients differ from usual *P. carinii* pneumonia in that there is primarily diffuse haziness all over the lung field concomittently, while the typical chest X-ray change of *P. carinii* include bilateral perihilar reticular shadow which progress to alveolar consolidation.[6] Additionally, a dramatic response to steroids and the fact that patients' symptoms worsened as steroids were tapered or omitted and improved again rapidly with retreatment imply an immunologic lung injury. Adding steroid to the medication for anti-pneumocystis carinii pneumonia is known

to be beneficial, but, the effect seems not so dramatic as in our patients. The observations in our cases suggest the possibility of chemotherapeutic agents, such as cytarabine, cyclophosphamide can lead to a drug-induced acute interstitial pneumonia in the absence of usual infection.

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국문초록

간질성 폐렴은 소아에서 비교적 드문 폐렴의 형태로서 바이러스나 *P, carinii*, 약물 등이 병인으로 생각된다. 고신대학교 복음병원에서 17, 20, 28 개월 전에 급성 림프구성 백혈병으로 진단되어 항암화학요법을 받고 있는 소아 환아들 중, 갑자기 발생된 호흡곤란증으로 내원했던 3명의 환아에서 영상 및 임상 소견상 원인미상의 간질성 폐렴으로 진단되었다. 입원 당시 환아들은 호흡곤란증이 심하여 조직검사나 기관지폐포세척술은 시행하지 못했으나, 혈액 및 구강 분비물에 대한 균 배양검사, mycoplasma, cytomegalovirus, Epstein-Barr virus의 혈청학적 검사는 음성이었다. 환아들에서 피부반점은 없었으며, 증상을 보이기 2주 전까지 사용했던 약물들은 Cytarabine, Cyclophosphamide, 6-TG, Vincristine, Dexamethasone, Methotrexate, 6-MP였다. 동맥혈가스 분석상 심한 저산소증과 흉부X선 소견상 양측성 미만성 젖빛유리 소견, 혈청내 총단백질의 감소를 보였고, 흉부CT 촬영을 했던 두 명 모두에서 ground glass attenuation을, 그 중 한 명에서는 소엽간 간질 비후(interlobular septal thickening) 소견을 보였다. 환아들은 산소흡입, 다수의 항생제, 항바이러스제, corticosteroid로 치료하였으며 이 중 coticosteroid를 중단했던 두 명에서는 호흡곤란증과 흉부X선 소견이 다시 악화되고 재사용시 다시 빠르게 호전되었다. 스테로이드 투여후 흉부X선 촬영소견상 초기의 미만성 폐음영 증가가 호전될 때 까지의 기간은 증례1에서 4일, 증례2에서 처음 입원시 3일, 두 번째 입원시 2일, 증례3에서 첫 시도시 3일, 중단후 악화되어 2차 시도시 6일 소요되었다. 세 환아에서 스테로이드의 총 투여 기간은 각각 24일, 12일, 16일이었으며 이후 이들은 다시 항암화학요법을 마치고 현재 모두 건강하게 생존하고 있다. 본 증례들에서 발생된 간질성 폐렴의 원인은 미상이나, 스테로이드 사용으로 임상증상과 X선 소견이 호전되는 점은 향후 유사 증례들의 병인연구나 치료에 참고가 될 것으로 생각된다.