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Acute Respiratory Failure in Systemic Lupus Erythematosus

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Abstract We reported a 15-year-old boy, who was well all along, presented to us with acute respiratory failure caused by acute lupus pneumonitis (ALP). The immediate differentiation of ALP from other causes of acute respiratory failure is of utmost importance. Early bronchoalveolar lavage for microscopic examination and microbiological study assists in arriving at the diagnosis. Early trial of immunosuppressive treatment in patients with ALP is life saving.

Key words Acute lupus pneumonitis; Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease, which may affect virtually every organ. Among various presentations, pleuropulmonary disease is uncommon in children. It has been reported that clinically significant pulmonary diseases only accounted for 3% and pleural diseases accounted for 17% at the onset of SLE in children.[1] While in adult series, 50% or more of the SLE patients would be affected some time during their course of illness.[1-4] The most common pleuropulmonary manifestation is pleuritis. Others include pleural effusion, chronic interstitial lung disease with fibrosis, pulmonary embolism, bronchiolitis obliterans, pulmonary vascular disease and diaphragmatic dysfunction.[1,3] Life threatening events like acute lupus pneumonitis or acute pulmonary haemorrhage are rare. We report a SLE patient who presented as acute respiratory failure and the approach to manage pulmonary emergency in lupus patients will briefly be discussed.

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Case Report

One week prior to admission, a 15-year-old boy who was previously well, complained of cough, breathing difficulty and progressive deterioration in exercise tolerance. He first noticed to have a small patch of macular rash over his right cheek 5 months prior to hospitalisation. He consulted several private practitioners but the rash did not respond to various local treatments. The rash persisted and became worse upon sun exposure. It spread to his cheeks, ears, fingers and toes. He started to have on and off fever one month prior to admission. He was treated with multiple broad-spectrum antibiotics, included erythromycin, cefuroxime and clarithromycin, but there was no response. He started to have non-productive dry cough five days prior to admission. He felt dizzy after walking up 3 flights of stairs and he complained of orthopnoea at night. Examination on admission showed that he was tachypnoic, and was cyanotic in air. While he was on nasal oxygen 2 L/min, his oxygenation was 92% and first arterial PaO_2 was 10.3 kPa, PCO_2 was 3.2 kPa. There were vasculitic rashes over his face with crusting, over his ears, hands, fingers and toes. There were diffuse papulonodular lesions over his back and right elbow, which subsequently was diagnosed to be papulonodular mucinosis by dermatologists. On examination of the chest, the air entry was satisfactory but there were diffuse crepitations with pleural rub. Fundoscopy showed cotton wool exudations over both eyes and other systems were uneventful. His first chest radiography (CXR) (Figure 1) showed diffuse patchy linear-reticular infiltrations and there was no pleural effusion.

Investigations showed haemoglobin 9.4 g/dL, white blood cell 3.7 x 10^9/L (lymphocyte 1.1 x 10^9/L and polymorphs 2.3 x 10^9/L). Direct Coomb's test showed positive polyspecific antibody (score 6), positive anti-IgG (score 6) and anti-C3 was negative. Erythrocyte Sedimentation Rate was 94 mm/hr. Anti-nuclear antibody (ANA) was 1:320 with speckled pattern; C3 0.24 g/L (normal 0.9-1.8 g/L); C4 0.06 g/L (normal 0.1-0.4 g/L); anti-dsDNA 218 IU/ml (normal <60 IU/ml), anti-Ro and anti-Sm antibodies were positive. C-ANCA and p-ANCA were negative. His clotting profiles and screening for lupus anticoagulants were negative. Anticardiolipin antibody (IgG) was 19 GPL u/ml (normal <10.0 GPL u/ml). Blood culture was negative. Serial viral titers including Mycoplasma pneumoniae were negative. Blood for CMV pp65 antigen was negative. Bronchioalveolar lavage (BAL) was performed 12 hours after admission. Differential count of the BAL showed 74% macrophages, 20.4% of lymphocyte, 5% plasma cells and 0.6% polymorphs. BAL for cytology did not show any malignant cells or haemosiderin-laden macrophage. BAL for rapid antigen test for respiratory syncytial virus (RSV), influenza, parainfluenza and adenovirus were negative. BAL sent for DEAFF test for cytomegalovirus (CMV) was negative. Subsequent viral culture did not show any growth. BAL for Gram stain and bacterial culture was negative. BAL for acid-fast bacilli (AFB) smear and subsequent AFB culture was also negative. Electrocardiogram and Echocardiogram were normal. There was no feature of pulmonary hypertension or pericardial effusion.

He was diagnosed to have lupus pneumonitis and was treated with oral prednisolone 20 mg three times a day (1.1 mg/kg/day). However, he showed progressive deterioration with increase requirement of oxygen up to 8 L/min through non-rebreathing mask (Figure 2). He was conscious and alert with good respiratory effort. He was treated with three doses of intravenous methylprednisolone 500 mg daily (10 mg/kg/day) and was followed by oral prednisolone at 20 mg three times daily (1.1 mg/kg/day). Figures 3 and 4 showed the progressive improvement in chest X-rays. At day 9 after admission, his CXR was normal (Figure 5) and his oxygen requirement weaned down to 1 L/min through nasal cannula. His follow up HRCT thorax and lung function test at 2 months after steroid therapy were normal. His spirometry test showed FVC 3.93 liter (reference FVC 3.8 liter), FEV1 was 3.54 liter (reference FEV1 3.42 liter). Diffusion test showed DLCO of 19.4 mL/mmHg/min (76% of predicted reference). After 4 weeks of high dose steroid, it was then tapered slowly to a low maintenance dose and azathioprine 100 mg (2 mg/kg/day) was added to control his lupus activity.

Repeated spirometry and HRCT thorax were normal. He was well with azathioprine and steroid for another 3 years until he had a lupus relapse with proteinuria and subsequent renal biopsy showed class IV lupus nephritis. He was treated with a course of cyclophosphamide and put into remission again.

Discussion

Our patient presented to us with photosensitive malar rash, vasculitic lesions, generalised papulonodular mucinosis, cotton wool exudates in fundi, together with

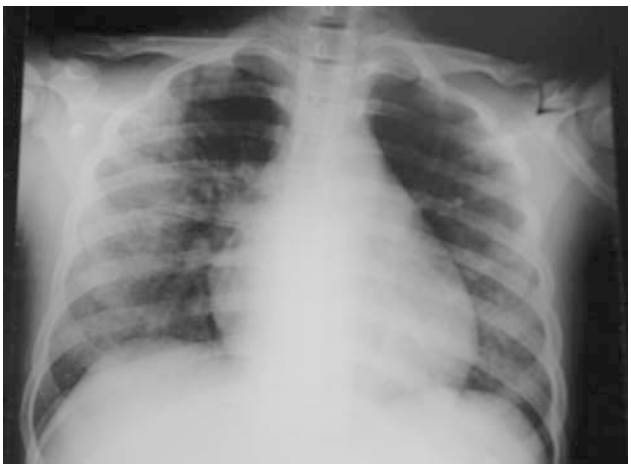

Figure 1 First CXR showed bilateral linear reticular infiltration. Patient's blood gas showed PaO_2 11 Kpa, PCO_2 4.15 Kpa while he was having 50% oxygen.

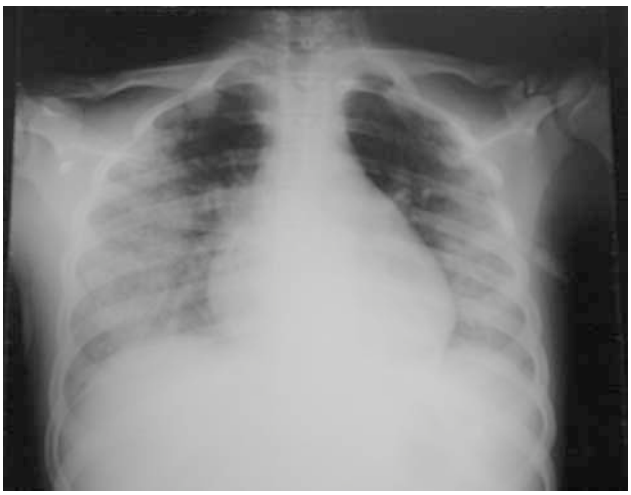

Figure 2 Patient showed progressive deterioration in respiratory distress. CXR showed increased pulmonary infiltration. Blood gases showed a drop of PaO_2 to 8 Kpa and PCO_2 4.6 Kpa while he was on 50% oxygen face mask. The oxygenation improved to 10 Kpa when oxygen was increased to 60% and was delivered through a nonrebreathing mask.

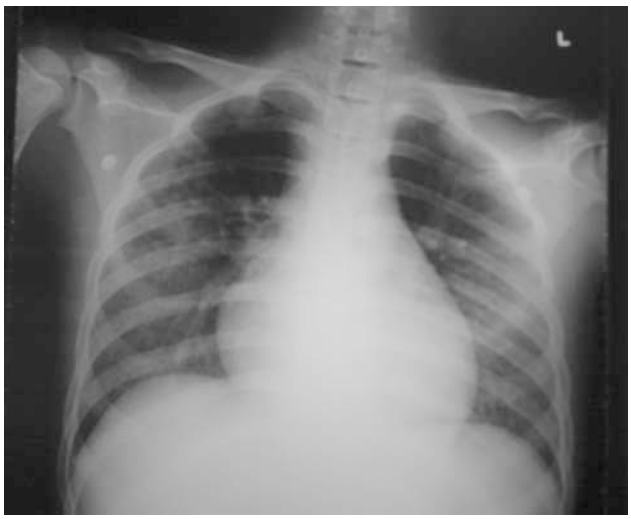

Figure 3 CXR taken 12 hours after first dose of methylprednisolone and it showed decrease in pulmonary infiltration. Oxygen requirement of the patient decreased to 5 L/min with PaO_2 improved to 11-13 Kpa.

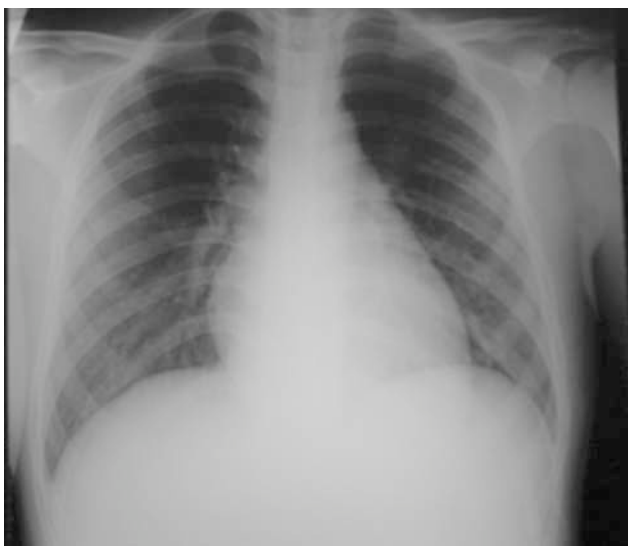

Figure 4 CXR taken on day 6 after admission. It showed clear up of pulmonary infiltration after three doses of intravenous methylprednisolone and he was taking oral prednisolone at 60 mg daily.

haematological and biochemical features of SLE as specified by the American College of Rheumatology.[4] On admission, he was in acute respiratory failure with tachypnoea and cyanosis. In the presence of chest crepitations, pleural rub and chest X-ray features of diffuse linear-reticular infiltrations over both lower lobes, the differential diagnosis on admission included acute lupus pneumonitis, pulmonary infections, pulmonary haemorrhage and pulmonary embolism. Careful

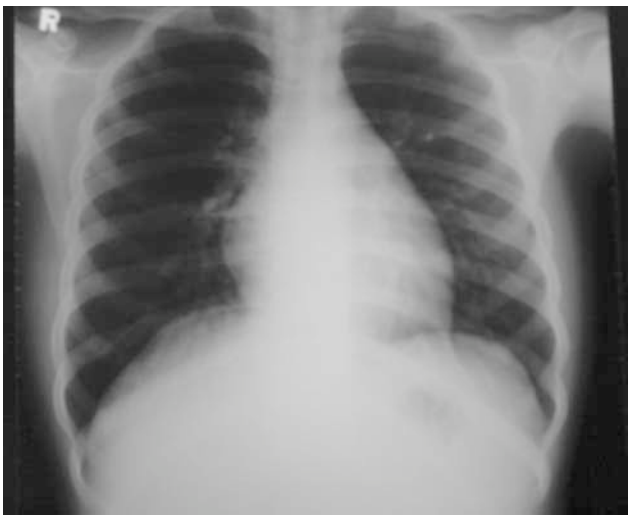

Figure 5 CXR was normal on day 9 after admission.

differentiation among them was mandatory because they differed in both treatment and prognosis.

Differential Diagnoses

Acute Lupus Pneumonitis

Acute lupus pneumonitis (ALP) is an abrupt febrile pneumonic process with a non-infectious etiology, which accounts for 9% of the total pleuropulmonary manifestations at the onset of SLE in childhood.[4,5] Most patients involved, as in our case, are young and have a relative recent onset of disease. Usually, they are in acute flare of SLE with multi-systems involvements.[6] Symptoms of ALP may mimic that of chest infection (fever, cough with scanty sputum, pleuritic chest pain, dyspnoea, tachypnoea and cyanosis). Crepitations and pleural rub may also be found. Chest X-rays may show patchy focal atelectasis/infiltrates (100%), pleural effusion (50%)[7] and elevation of both hemi-diaphragms. Arterial hypoxemia may be detected. However, no causative organism can be isolated and the histopathology is non-specific. High dose corticosteroid is the mainstay of treatment.[1,6,7]

Infections

SLE patients are particularly prone to broncho-pneumonia. It has been showed that respiratory tract infection is the third leading cause of death in SLE patients, with sepsis being the first and renal failure being the second.[4] This is partly due to the intrinsic immunological defect of SLE patient and partly due to the local environmental conditions of the lung, e.g. lung edema and weak respiratory muscles, which favour the growth of pathogenic organisms. However, the use of corticosteroid and immunosuppressive

agents remain the major contributory factors.[1,7,8]

SLE patients, especially those on treatment are in a relative immunocompromised state. They are prone to bacterial, viral, fungal and protozoan infection. Most commonly seen organisms, which cause opportunistic infections are Aspergillosis, Cryptococcus, Pneumocystis Carnii, Cytomegalovirus and Nocardia. Among them, Nocardia Asteroids infection is notorious to cause pulmonary infiltrations, pleural effusions and central nervous system abnormalities, which can be confused with the clinical manifestation of lupus itself. Co-infection by both Pneumoncystis Carnii and Cytomegalovirus had been reported and was associated with poor prognosis.[9] Tuberculosis is an important differential diagnosis especially in endemic area in Hong Kong.

Clinical features of chest infection are similar to that of ALP. Identification of causative organisms in sputum or blood culture is the key for diagnosis. Bronchoalveolar lavage and lung biopsy may help in obtaining the necessary sample. Board spectrum antibiotics should be administrated empirically whenever there is new lung infiltrate until infection has been ruled out. Since bacterial and viral cultures are time consuming, rapid antigen studies are useful in excluding some of the opportunistic infections. Though they have their own limitations, their results are valuable in acute emergency.

Our patient was having active systemic lupus disease at presentation. Without a prior treatment with steroid or immunosuppressive agents and absent of positive evidence for an infection, acute lupus pneumonitis was the likely diagnosis. Although superimposed chest infection was not always easy to exclude, every attempt should be tried to differentiate them. Rapid antigen studies, Gram stain and AFB smear obtained from sputum & BAL samples in our patient helped to exclude chest infection, however the list of organism is never exhausted. Board spectrum of antibiotics had been commenced on admission yet our patient's condition continued to deteriorate. Hence, a trial of pulse steroid was put forward.

Acute Pulmonary Haemorrhage

Acute pulmonary haemorrhage is a rare presentation of SLE, which carries a high mortality of more than 50%.[1-3,8,10] It usually affects young females[2] and those who are on acute flare of long standing SLE. These patients usually have clinical and laboratory evidence of multi-system involvements, including positive anti-DNA antibodies and hypocomplementemia.[1,7,8] The presentation of pulmonary haemorrhage is similar to that of ALP. However, it runs a rapid deteriorating course and the patients characteristically present with haemoptysis and anemia. For those without frank haemoptysis, a great drop in haemoglobin or haematocrite level together with bilateral pulmonary infiltrate of alveolar pattern on CXR should alert one to this possibility. Bronchoscopy allows direct examination of the airway. The presence of fresh blood, blood clots or haemosiderin-laden macrophage with the absence of purulent sputum and organisms favor the diagnosis of pulmonary haemorrhage .[8] Histopathology is non-specific in most cases. The more characteristic histo-pathological features of alveolar haemorrhage with extensive filling of the alveolar spaces with red cells and fibrin, and grossly apparent vasculitis or necrosis are rarely seen.[1] Therefore, open lung biopsy is of limited use. Intensive supportive measures are mandatory. High dose "pulse" steroid is the mainstay of treatment.[1,2,8] Cyclophosphamide or plasmapharesis can be considered in refractory cases.[1,8,10]

In the absence of haemosiderin-laden macrophage in BAL and a stable hemoglobin level, acute pulmonary haemorrhage was less likely in our patient. The rapid response to steroid and rapid clearing up of his lung infiltrate also supported the diagnosis of ALP rather than acute pulmonary haemorrhage.

Pulmonary Embolism

Pulmonary embolism should be suspected in lupus patient who have lupus anticoagulant and/or antiphospholipid antibodies with respiratory symptoms, especially pleuritic chest pain and dyspnoea. It had been shown that the prevalence of thrombosis increased from 10% to 30% in patients who were positive for anticardiolipin ãntibodies titer.[1,8,10] Clinical features of pulmonary embolism depend on the degree of obstruction. With massive pulmonary embolism, there will be sign of right ventricular failure with acute circulatory collapse. Pleuritic pain, dyspnoea, haemoptysis, pleural rub, crepitations and tachypnoea may be present in less severe cases. For chronic thromboembolism, pulmonary hypertension is likely to be the consequence. CXR is usually normal, but it may show non-specific features like pulmonary infiltrates, atelectasis, radiolucent areas due to oligaemia, pulmonary artery enlargement and abrupt cut off of vessels. Electrocardiogram (ECG) may show characteristic S1Q3T3 pattern. Arterial hypoxemia is present in majority of cases. Pulmonary angiogram and ventilation-perfusion scan are the gold standards for diagnosis. Spiral CT can also be helpful. Anticoagulant is the mainstay of treatment. The use of corticosteroids or immunosuppressive agents as adjuvant should be considered to decrease circulating antibodies.[1] The placement of inferior vena cava filter should be considered in individual cases.[2]

SLE patients especially those with positive anticardiolipin antibody (IgG), like our patient, are at increase risk for coagulation problem. Except a mild increment of anticardiolipin antibody, the clotting profile and test for lupus anticoagulants were normal in our patient. Although a lung perfusion scan was not performed in our patient, a normal ECG and echocardiogram make the diagnosis of pulmonary embolism unlikely.

Role of Bronchoalveolar Lavage in Diagnosis and Management of ALP

Bronchoalveolar lavage (BAL) is an effective and relatively safe procedure for the recovery of cellular component and mediators from the lower respiratory tract for analysis. It yields valuable information and may help diagnosis in cases like infection.

There is no specific BAL finding for the diagnosis of ALP. The main role of BAL is to help in ruling out differential diagnosis like chest infection and pulmonary haemorrhage. It has been showed to have good sensitivity in detecting opportunistic infection like Pneumocystic carnii.[2] The quantitative cultures from the BAL fluids are also helpful in establishing the etiology of bacterial pneumonia. The presence of blood or haemosiderin laden macrophages would suggest pulmonary haemorrhage. The presence of haemosiderin in macrophages suggests that pulmonary haemorrhage has occurred for more than 48 hours.

Role of High Resolution CT Scans in Diagnosis and Management of ALP

It has been shown by multiple studies[6] that high resolution CT scan (HRCT) is a sensitive means of detecting interstitial lung disease. It allows the identification of asymptomatic patient but the significance of which has to be explored and correlated with BAL and lung biopsy. Since the extent of morphological changes in HRCT correlates with the severity of impairment of the diffusing capacity, it allows a rough estimation of the degree of lung impairment. Serial HRCT serves as a good means for monitoring the disease progress but it's role in pinpointing the diagnosis is limited.

Role of Lung Biopsy in Diagnosis and Management of ALP

Lung biopsy, both trans-bronchial and open biopsy, is a relative invasive method of investigations. It had been shown by a retrospective review study that a specific diagnosis could be reached in 64% of all biopsies done in children for investigations of pulmonary diseases.[11] However, since the histo-pathological features (acute alveolar wall injuries, alveolar haemorrhage, alveolar edema, hyaline membrane formation and small vessel vasculitis)[2,8] of ALP are neither specific nor pathonomonic, the main role of lung biopsy is to rule out infection when other means are proven futile.[7]

Although open lung biopsy (OLB) has been the standard for evaluation of interstitial lung disease in the past, such invasive procedure is not without risk. It is best to be avoided in patients who suffer from acute respiratory failure because it has been shown to be associated with high morbidity and mortality in such circumstance. The overall complication rate for OLB in children was around 51% with pneumothorax, lung collapse and bleeding being the most commonly encountered problems. In addition, immediate post-operation mechanical ventilation would be necessary in all patients with acute respiratory failure. Weaning failure and recurrent pneumothoraces were commonly encountered problems.[11]

Treatment Options for ALP

Due to the rarity of ALP, there has not been any randomised control trial of different treatment modalities. Therefore, current management is mainly based on pervious experience and no consensus has been reached.[3,12]

When a new pulmonary infiltration is present in a lupus patient, aggressive investigations has to be done to rule out chest infection. Broad spectrum antibiotics should be started empirically and its administration should not be delayed by investigations. When ALP is suspected, 1-2 mg/kg of prednisolone or equivalent per day is recommended.[1,6,7] Most patients respond well to such regime but some may experience relapse or even progress to chronic interstitial pneumonitis. In case of respiratory failure, more aggressive treatment including "pulse" methylprednisolone (1 g IV for 3 to 5 days)[6,7] and/or high dose intravenous cyclophosphamide is recommended. Plasmapheresis may be given as an adjunctive therapy. For refractory cases, cyclophosphamide, azathioprine and methotrexate may be considered.[1,2,6,7] Duration of treatment should be made according to an individual's clinical condition and response.

Without a lung biopsy, ALP was a diagnosis of exclusion in our patient. A lung biopsy during the critical situation might be dangerous and a definitive diagnosis was not guaranteed by histology. Our patient showed marked improvement with intravenous methylprednisolone and

high dose oral Prednisolone. The initial dose of pulse methylprednisolone was low as compared with 1 gm/day as preliminary result for sepsis work up were lacking when steroid was started. Since he showed dramatic improvement with a dose of 10 mg/kg/day and so the same dose was continued for another 3 days. He was medically fit for discharge after 10 days of hospitalisation. No mechanical ventilation was needed. Azathioprine was added to taper steroid dosage and he remained well with no respiratory symptom and good exercise tolerance.

Prognosis and Complications of ALP

The overall prognosis for ALP is poor with 50-90% mortality despite treatment.[1] Prompt identification and treatment are essential for survival during the acute phase. For those who survived the acute episode, 50-100% would eventually progress to chronic interstitial pneumonitis.[6,7]

Chronic interstitial pneumonitis can develop at any time. It can be divided into 2 main groups: the more common group, which has an insidious onset of disease, and the less common group, which develops after an acute episode of ALP.[7,10] The prevalence of symptomatic chronic interstitial pneumonitis has been reported to be 3%.[6,7] The percentage is expected to be higher if asymptomatic patient is taken into account.[6,7] These patients are predominantly male with late-onset SLE.[6] They may have fever, non-productive cough and progressive shortness of breath. Cyanosis and crepitations can be detected. Both spirometery and lung-volume measurement will show restrictive defect or loss of ventilable lung volume without obstruction to airflow and results in ventilation-perfusion mismatch.[7] HRCT is very sensitive in diagnosis of the disease and abnormal changes can be detected in asymptomatic cases. It also allows a reasonable prediction of responsiveness to treatment. Patient with a ground glass and alveolar consolidation detected in HRCT will be more likely to be steroid-sensitive. However, those with severe honeycomb lesion on the HRCT scans are less likely to be treatment responsive.[7] High dose steroid for at least 6-8 weeks is suggested. It should be tapered depending on the clinical and laboratory responses of the patient. Immunosuppressive agents such as azathioprine and cyclophosphamide should be considered in patients who fail to response satisfactorily to steroids.[1,7] Unfortunately, favourable response occurred only in 15-30% of patient with chronic interstitial lung disease. Complete remission occurred in less than 5%.[1]

Conclusion

Acute respiratory failure due to acute lupus pneumonitis is an uncommon presentation of SLE. High index of suspicious is needed for its recognition. The early use of BAL helps to rule out opportunistic infection and haemorrhage, and assists in early diagnosis and treatment.

References

1. Orens JB, Martinez FJ, Lynch JP 3rd. Pleuropulmonary manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 1994;20:159-93.
2. Lawrence EC. Systemic Lupus Erythematosus and The Lung. In: Lahita RG, editor. System Lupus Erythematosus, Fourth Edition. Elsevier Academic Press, 2004:961-74.
3. Ciftci E, Yalcinkaya F, Ince E, et al. Pulmonary involvement in childhood-onset systemic lupus erythematosus: a report of five cases. Rheumatology (Oxford) 2004;43:587-91.
4. Petty RE, Laxer RM. Systemic Lupus Erythematosus. In: Cassidy JT, Petty RE, editors. Textbook of Pediatric Rheumatology, Fifth Editon. Elsevier Saunders, 2005:342-91.
5. Delgado EA, Malleson PN, Pirie GE, Petty RE. The pulmonary manifestations of childhood onset systemic lupus erythematosus.Semin Arthritis Rheum 1990;19:285-93.
6. Cheema GS, Quismorio FP Jr. Interstitial lung disease in systemic lupus erythematosus. Curr Opin Pulm Med 2000;6: 424-9.
7. Quismorio FP, Jr. Pulmonary Manifestations of Systemic Lupus Erythematosus. In: Wallace DJ, Hahn BM, eitors. Dubois' Lupus Erythematosus, Fifth Editon. Williams & Wilkins, 1997: 673-92.
8. Keane MP, Lynch JP 3rd. Pleuropulmonary manifestations of systemic lupus erythematosus. Thorax 2000;55:159-66.
9. Ku ASW, Lee KW, Wan KL, Chan WKY. Coexisting pneumocystis carinii and cytomegalovirus pneumonia in systemic lupus erythematosus. HK J Paediatr (new series) 1999; 4:101-3.
10. Boumpas DT, Austin HA 3rd, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic Lupus Erythematosus: Emerging Concepts: Part 1: Renal, Neuropsychiatric, Cardiovascular, Pulmonary, and Hematological Disease. Ann Intern Med 1995 15;122:940-50.
11. Davies L, Dolgin S, Kattan M. Morbidity and mortality of open lung biopsy in children. Pediatrics 1997;99:660-4.
12. McIntosh JC, Mroczek EC. Pathological cases of the month. Lupus pneumonitis: acute inflammation superimposed on long-standing disease. Arch Pediatr Adolesc Med 1994;148: 207-8.