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Case Report

Coexisting Pneumocystis Carinii and Cytomegalovirus Pneumonia in Systemic Lupus Erythematosus

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Abstract Opportunistic infection with multiple organisms is known to occur in immunocompromised patients. In this article, we report a 14 years old girl, with 4 years history of systemic lupus erythematosus, who developed pneumonia caused by Pneumocystis carinii and cytomegalovirus. She responded to combination therapy of intravenous sulfamethoxazole-trimethoprim and ganciclovir. She shared some common risk factors in SLE for developing Pneumocystis carinii pneumonia, including active disease with renal involvement, history of receiving immunosuppressant, and lymphopenia. The author recommends the early use of bronchoalveolar lavage to investigate pneumonia in immunocompromised patients.

Key words Pneumocystis carinii; Cytomegalovirus; Systemic lupus erythematosus

Introduction

Pneumocystis carinii pneumonia (PCP) is a well-known infection in immunocompromised patients with high mortality. PCP has been reported both in adult and paediatric patients with systemic lupus erythematosus (SLE). Patients with SLE are prone to develop opportunistic infection due to both the disease process and the medical therapy. Cytomegalovirus (CMV) may coexist with PCP pneumonia in immunocompromised host, which is associated with poorer prognosis. As specific drugs are available for these organisms, early diagnosis and treatment are important. The early use of bronchoalveolar lavage (BAL) in the diagnosis of pneumonia in immunocompromised patients is recommended.

Case Report

A 14-year-old Chinese girl with SLE presented at 10 years old with fever, arthralgia, skin morphea, uveitis, proteinuria and anaemia. Renal biopsy revealed WHO Class IV glomerulonephritis. She was treated with prednisone and azathioprine. She developed relapse of lupus nephritis with hypertension 3 years after presentation. She was treated with intravenous pulse methylprednisolone (30mg/kg/d) followed by high dose oral prednisone 60mg/d for 6 weeks. She also received a course of oral cyclophosphamide followed by azathioprine 50 mg/d. The dose of prednisone was tailed down to 37.5 mg/d afterwards. She stayed in hospital for twelve weeks totally.

Six days after discharge, she was readmitted because of one-day history of fever, cough and dyspnoea. Physical examination revealed prominent Cushingoid features with tachypnoea and decreased air entry. There was hypoxaemia despite on high-inspired oxygen, but without hypercarpnia. Chest X-ray revealed bilateral diffuse interstitial shadow. She was intubated and BAL was performed. In view of the high likelihood of Pneumocystis carinii pneumonia, intravenous sulfamethoxazole-trimethoprim 120 mg/kg/d was started immediately after BAL. Intravenous ganciclovir and ceftazidime were empirically started, as she was prone to other opportunistic infections and she had history of prolonged hospital stay recently. The oxygenation index was 10.7 initially. Blood investigation on admission revealed lymphocyte 0.1×10^9/L, platelet 95×10^9/L, haemoglobin 6.7 g/dL, urea 13.4 mmol/l, creatinine 175 μmol/l. Her creatinine clearance was 17 ml/min/1.73m^2. Her anti-ds DNA antibody titer, C3 and C4 level were normal. C-reactive protein was increased to 114 mg/l.

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Her fever subsided soon afterwards. On the next day, the silver-stain detected Pneumocystis carinii in BAL. The oxygenation index improved to 4.9 on day 3. Ganciclovir was stopped on day 3 as Pneumocystis carinii was thought to be the causative organism. As the BAL fluid did not reveal any positive result for bacteria, fungi, or acid fast bacilli, and other site of sepsis was not identified, ceftazidime was stopped after 8 days of therapy.

However, there was no clinical improvement in her respiratory condition. She required progressive increase in oxygen requirement. On day 7, CMV was positive from BAL, both in antigen test and viral culture. The CMV titer was increased to 1:320. Therefore ganciclovir 7.5 mg/kg/d was started again. Lung biopsy was withheld because of thrombocytopenia with platelet 59 x 10^9/L and prolonged aPTT of 63.2sec. Ventilator support could be weaned down and she was successfully extubated on day 11. Both the doses of sulfamethoxazole-trimethoprim and ganciclovir were reduced as bone marrow suppression developed.

She deteriorated again after extubation with progressive impairment in oxygenation. Chest X-ray revealed bilateral lower zone hazziness. Tracheal aspirate before extubation revealed heavy growth of Candida species with presence of white cells. Amphotericin B was then commenced on day 12. Her chest condition improved after addition of amphotericin B. Supplementary oxygen could be weaned off on day 17.

Intravenous sulfamethoxazole-trimethoprim was stopped on day 16 and was changed to oral prophylactic dose. Ganciclovir and amphotericin B were stopped on day 20. Blood count on day 33 revealed platelet 166 x 10^9/L, lymphocyte 0.7 x 10^9/L, and haemoglobin 8.7 g/dL. She was discharged from hospital on day 44, and put on prednisone 40 mg/d, oral sulfamethoxazole-trimethoprim prophylaxis, labetalol and nifedipine for her hypertension.

Discussion

Pneumocystis carinii is a pulmonary opportunistic organism. In healthy persons, subclinical infection during early childhood may occur, resulting in low antibody titers. Clinical disease occurs later due to reactivation of latent infection. A multi-center evaluation of 1103 patients with SLE showed that infection was the main cause of death in 33%, while active disease was the second cause of death in 31% of them.[1] So the early diagnosis and treatment of opportunistic infection is important. Clinicians should have high index of suspicion.

BAL is a very useful method in the diagnosis of opportunistic infections. It can detect PCP in more than 80% of case. In our patient, BAL was performed on the day of deterioration and the positive result of silver-stain was available in one day. Therefore high dose intravenous sulfamethoxazole-trimethoprim could be commenced in the earliest time. BAL should be considered early in immunocompromised patients with pneumonia. Lung biopsy can provide more definite identification of the causative organism and is helpful in those BAL-negative cases.

In children, PCP occurs most frequently in association with leukaemia and other malignancy. In adults with SLE, risk factors for PCP included active disease, high steroid dose >40 mg/day, use of cyclophosphamide or azathioprine within the previous 6 months, and severe lymphopenia <0.35 x 10^9/L.[2] The exact incidence of PCP in paediatric SLE is unknown and the analysis of PCP in paediatric SLE is limited in literature.

Foster et al reported 3 pediatric SLE patients who shared some risk factors that have been described in adult SLE. All had severe SLE activity requiring prednisone and azathioprine with lymphocyte count <1.5 x 10^9/L, but none had severe lymphopenia <0.35 x 10^9/L. CD4 level was low in one of the patient.[3] Walravens and Chase reported a paediatric SLE patient with renal involvement, who succumbed after renal transplantation due to PCP and E. coli septicaemia.[4] Fish et al reported 2 children having lupus nephritis whom developed PCP, and one of them died.[5] All these patients were put on prednisone and azathioprine.

Fortenberry and Shew reported a 16 years old adolescent with SLE who died of PCP within 3 months of diagnosis.[6] The dose of steroid was never more than 40 mg/d and cytotoxic agents were not used in this patient, but the lymphocyte count was not mentioned. Our patient shared some common risk factors including renal involvement, lymphopenia with lymphocyte count 0.1 x 10^9/L, history of treatment with high dose prednisone and immunosuppressants including azathioprine and cyclophosphamide.

In view of the high effectiveness of prophylactic therapy in patients at risk for PCP, it may be considered in some high-risk SLE patients. Porges et al proposed that severe lymphopenia (<0.35 x 10^9/L) could be used to define a subgroup of high risk adults with SLE and consider prophylactic therapy.[2] However, another report suggests that secondary chemoprophylaxis against recurrent PCP may not be absolutely indicated in patients with connective tissue disease.[7] Intermittent oral chemoprophylaxis is effective in children with malignancy and those with AIDS. The side effect from drug reaction is usually mild and well tolerated. However, there were no well-defined reliable predictors of PCP in children with SLE to guide for commencement of chemoprophylaxis. The role of chemoprophylaxis in paediatric age group remained controversial.

The possibility of co-existent infections with more than one organism should be considered in immunocompromised patients. CMV is a well-known agent. The fatality of CMV pneumonia can be up to 85%. CMV infection can exacerbate SLE and increase the susceptibility to opportunistic infection. However, the diagnosis of CMV pneumonia is often difficult to make because subclinical infection may be present in immunocompromised patients, and CMV may be isolated from sputum in those without active infection. The sensitivity of viral isolation from BAL for diagnosis of CMV pneumonia was 61% and specificity was 100%.[8] Concomitant assay of polymerase chain reaction for CMV and viral antibody titer may be preferable in making a conclusive diagnosis.[9] CMV pneumonia usually associates with high levels of antigenaemia or viraemia, and clinical symptom.[10] In our patient, CMV pneumonia was suggested by the presence of CMV in BAL with an increased serological titer of 1:320, and the patient showed response when ganciclovir was added, although lung biopsy was not performed because of bleeding diathesis.

Candida infection is another well-known opportunistic infection. Candidiasis is the most frequent systemic fungal infection in immunocompromised hosts. It may manifest clinically as local or disseminated infection. The diagnosis of Candida pneumonia may be sometimes difficult to make because the finding of Candida in sputum is not diagnostic. Blood culture rarely yields the organism and serological test is not sufficiently sensitive and specific. The sensitivity of BAL in detecting histological proven fungal disease was only 59% and high resolution CT scan is used to increase the detection rate.[11] Lung biopsy may be necessary to demonstrate the yeast and pseudohyphal form. In our patient, Candida was isolated in tracheal aspirate without definite histological proof at that time. The diagnosis of Candida pneumonia may be dubious although her condition improved after commencement of amphotericin B and did not require reintubation.

Bone marrow suppression is a significant concern as a side effect from medication, which may further jeopardize the already impaired immunity. It was evident in our patient after the combination therapy of sulfamethoxazole-trimethoprim and ganciclovir, which was reversible after reduction of dosage.

In conclusion, opportunistic infections caused by multiple organisms may be present in patients with SLE receiving corticosteroid and immunosuppressants. High index of suspicion should be maintained when treating respiratory symptoms in these patients. The authors recommend the early use of BAL to investigate pneumonia in immunocompromised patients.

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