PNEUMOCYSTIS JIROVECII PNEUMONIA IN A PATIENT WITH ANTI-*N*-METHYL-D-ASPARTATE RECEPTOR POSTHERPETIC ENCEPHALITIS

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Abstract: Anti-*N*-methyl-D-aspartate receptor encephalitis is a neuroimmunologic disorder that has been increasingly diagnosed during the past 5 years. It provokes a predictable syndrome treated with several immunomodulatory agents, such as corticosteroids and/or biologics. We managed a child with this disease who developed *Pneumocystis jirovecii* pneumonia as a direct infectious complication of the use of rituximab.

Key Words: rituximab, *Pneumocystis jirovecii*, children, pneumonia, anti-NMDAr encephalitis

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Anti-*N*-Methyl-D-Aspartate receptor (NMDAr) encephalitis has been recognized as the second most common autoimmune encephalitis in children after acute demyelinating encephalomyelitis.[1] In NMDAr encephalitis, patients develop cerebrospinal fluid (CSF) antibodies against NMDAr, a neuronal synaptic receptor leading to inactivation of GABAergic pathways and modifications of the dopaminergic, noradrenergic and cholinergic systems. This explains a constellation of signs, such as autonomic instability, dyskinesias, psychiatric disorders, dystonia, seizures and speech disorders. Although clinical relapses are not uncommon, it has been estimated that partial or total recovery is observed in up to 80% of patients. The treatment usually includes the sequential administration of corticosteroids and intravenous (IV) immunoglobulin or even plasma exchange, among others.[2] However, complications derived from these inmunomodulatory agents when treating this disorder are yet to be established.

We describe a case of an infant who developed respiratory failure due to *Pneumocystis jirovecii* pneumonia while receiving treatment for NMDAr + postherpetic encephalitis.

CASE REPORT

An 11-month-old male recently diagnosed with herpes simplex virus 1 (HSV-1) encephalitis developed low-grade fever and fussiness 24 hours after completing a 21-day course of IV acyclovir which prompted his readmission to the inpatient ward. He was born at 39 weeks of gestational age, via C-section due to uterine myoma to nonconsanguineous parents (Gravida 2 Para 0 Abortion 1). The pregnancy was controlled and his birth weight was 3730 g (75–90 percentile for age).

On admission, he had been fussy and inconsolable for the past 10 hours, so a lumbar puncture was performed with concerns of HSV reactivation. CSF showed mild pleocytosis with 81.7 mg/dL proteins, 54 mg/dL glucose, 298/mm^3 red blood cells, 74/mm^3 white blood cells (lymphocytes 95%, polymorphonuclears 5%), Gram stain was negative. HSV DNA polymerase chain reaction (PCR) in the CSF was negative. Twenty-four hours after admission, the patient developed altered mental status along with choreoathetoid movements. Anti-NMDAr antibodies were detected in serum and CSF. Treatment with immunoglobulin (1 g/kg/d); and methylprednisolone (initial dose 30 mg/kg/d) was initiated and slowly tapered over 90 days. On day 17th of his illness due to the lack of response, rituximab (375 mg/m^2) was initiated once a week for 4 weeks. Anti-NMDA antibodies cleared from blood and CSF but he developed profound B cell lymphopenia (0%). He did not improved clinically, therefore 2 weeks later IV cyclophosphamide (2 doses of 750 mg/m^2, with an interval of three weeks) was initiated, also with limited response as he continued with persistence of choreoathetosis and altered mental status.

Between the first and second dose of cyclophosphamide, the patient developed low-grade fever and empirical antimicrobials were initiated with concerns for a possible central line-associated blood stream infection as the patient had a peripherally inserted central catheter line placed since day 9th of hospitalization. He received vancomycin (60 mg/kg/d), cefepime (50 mg/kg/8 h) and amphotericin B (3 mg/kg/d). Serum C-reactive protein was 20 mg/L and procalcitonin (PCT) 1.1 ng/mL.

Four days after the last dose of cyclophosphamide, he developed acute respiratory distress with severe hypoxemia (transcutaneous $SatO_2$ 50%), and was transferred to the Pediatric Intensive Care Unit where supplemental oxygen via a nonrebreather mask was initiated. He was placed in contact and droplet isolation. His temperature was 37.8°C. On physical examination, he presented mild tachypnea (42 bpm) and severe hypoxemia ($SatO_2$ 85% to FiO_2 1). Malaise and cutaneous pallor was observed. On auscultation, he had a good air entrance bilaterally with scattered rhonchi. His neurologic exam continued to reveal altered mental status with generalized choreoathetoid movements. The rest of physical exam was within normal limits. His respiratory status continued to deteriorate and noninvasive ventilation (BiPAP mode with FiO_2 1) was initiated. Twelve hours after admission, his O_2 needs were weaned to FiO_2 0.5. Initial laboratory results revealed a C-reactive protein of 80.9 mg/L and PCT of 22.83 ng/ml. Lymphopenia (1410/μL) was confirmed, with the rest of the complete white blood cell count and serum biochemistries being within normal limits, except for severe hypokalemia (1.7 mEq/L). Imipenem (25 mg/kg/6 h) and amikacin (5 mg/kg/8 h) were then added to his antimicrobial regimen. His respiratory distress worsened and 24 hours after the Pediatric Intensive Care Unit admission he was intubated and mechanically ventilated requiring nitric oxide and inotropic support with dopamine and dobutamine. A chest radiography showed bilateral and bibasilar alveolar infiltrates, suggestive of acute respiratory distress syndrome. Due to the severe lymphopenia, empiric treatment with IV trimethropim-sulfamethoxazole (TMP-SMX) in a dosage of 20 mg/kg/day was added.

A bronchoalveolar lavage was performed 48 hours later where *Pneumocystis jirovecii* DNA was identified by PCR (*Cytomegalovirus* PCR was negative). Methyl-prednisolone IV at 2 mg/kg/day was initiated. A progressive improvement of inflammatory parameters and oxygenation indices was observed over the next 10 days, as well as a slow decrease in respiratory support needs.

On day 7 post admission to the Pediatric Intensive Care Unit, lymphocyte populations were studied, revealing a total absence of B lymphocytes and panhypogammaglobulinemia (absolute count 1360/μL, CD4: 846/μL, CD8: 423/μL, CD16/CD56: 53/μL, CD19: 0/μL, IgA <0.05 g/L; IgG 1.65 g/L and IgM of 0.09 g/L). Mutations on the Toll-like receptor 3 or UNC93B deficiency were not studied.

DISCUSSION

Pneumocystis jirovecii is responsible for causing pneumonia (*Pneumocystis jirovecii* pneumonia [PJP], *Pneumocystis pneumonia*) in immunocompromised hosts. This microorganism

is transmitted by person-to-person via the airborne route, achieving a high rate of respiratory tract colonization during the first years of life. In fact, nearly 85% of healthy infants will have seroconverted by the age of 20 months.[3] Fulminant respiratory failure and fever are the most frequent forms of presentation. The main risk factor to develop PJP is lymphopenia in the context of primary or secondary immunodeficiency, often associated with the use of immunosuppressive medications such as those used in patients with cancer or after solid organ or bone marrow transplantation. In HIV infection the risk is higher, particularly in children ≥6 years old with CD4 counts <200 cells/mm^3, in children 1 to <6 years old with CD4 counts <500 cells/mm^3 and in all infants <12 months old regardless their CD4 count. Therefore, prophylactic TMP-SMX is indicated in these situations. Our patient developed severe PJP in the context of profound lymphopenia associated with the use of rituximab. To our knowledge, this is the first case reporting such complication in an infant receiving treatment for NMDAr encephalitis.

Rituximab is a monoclonal antibody directed against the CD20 primarily found on B cells that has been used for the treatment of resistant NMDAr encephalitis. It can cause B cell depletion by one or more of several antibody-dependent mechanisms, such as Fc receptor-mediated antibody-dependent cytotoxicity, growth arrest and B cell apoptosis.[4]

It has been suggested that CD20+ cells play a critical role in generating protective CD4+ T-cell immune responses against *Pneumocysis.* In immunodeficient mice anti-CD20 treatment was associated with potential impairment of CD4+T-cell responses, decreased production of IFN-γ and had greater susceptibility to *Pneumocystis* (identified 4 weeks after *Pneumocystis* inoculation, as they had higher infectious burden in the lungs than the control mice).[5]

In a recent multicenter retrospective study that was conducted to assess the infectious complications associated with the use of rituximab in pediatric autoimmune and inflammatory central nervous system diseases, only 7.6% of the study participants developed infectious diseases complications. Of the 144 patients, 1.4% developed a pneumonia severe enough to require hospitalization and/or IV antibiotics, but none of them were classified as a potential life-threatening or disabling complication. Interestingly, only 18% of the cohort received prophylactic antibiotics, being TMP-SMX the agent most frequently used, thus it remains unclear the potential reduction of the risk for PJP infection in those patients.[6]

Another retrospective study identified a cohort of 30 adults that had undergone therapy with rituximab and developed PJP. The overwhelming majority (90%) of these patients had received concomitant immunosuppressive therapy (chemotherapy and/or glucocorticoids) and just one patient was receiving prophylactic TMP-SMX. None of the underlying diseases was an autoinflammatory central nervous system disease.[7] To adequate management of children with neuroimmunologic conditions under regimens including rituximab, it has been suggested to initiate CMV prophylaxis in high-risk patients (those with combined immunosuppressive therapies), whereas prophylaxis for PJP is not recommended.[8]

TMP-SMX at 20 mg/kg/d is the first-line therapy for PJP. While glucocorticoids are frequently used as an adjunctive therapy, its potential benefit in PJP in non-HIV infected patients remains controversial.[9] The mortality rate without any treatment is 90% to 100%, decreasing to 30% if adequate antibiotic therapy is promptly initiated. A better outcome is attained among HIV-infected patients (10%–20% of mortality). Our patient received TMP-SMX only after he developed severe hypoxemia and respiratory failure with positive outcome.

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PYOGENIC LIVER ABSCESS WITH DELAYED PRESENTATION AFTER APPENDECTOMY

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Abstract: Liver abscess is a serious condition that is uncommon in otherwise normal children. Predisposing factors include immunosuppression, surgery and travel to certain areas. We present a patient with liver abscess 4 months after appendectomy. In addition, we reviewed 7 cases of liver abscess that occurred in a 22-year period.

Key Words: liver abscess, appendicitis, percutaneous drainage, delayed abscess

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Pyogenic liver abscess is rare in healthy children and occurs mostly in immunocompromised children with chronic granulomatous disease or leukemia. Historically, appendicitis was a common cause of pyogenic liver abscess, but with the routine administration of antibiotics and early surgical intervention, this cause has declined drastically.

The case of a girl with an extensive pyogenic liver abscess 4 months after appendectomy prompted us to review all cases of pyogenic liver abscess in children <15 years of age admitted to our hospital in a period of 22 years. The aim of this case is to raise awareness of this potential late complication and discuss the etiology and management options of pyogenic liver abscess.

CASE REPORT AND CHART REVIEW

A 14-year-old girl presented to the emergency department of La Fe Hospital, a tertiary care center with 200 pediatric beds, with