We describe our experience regarding metronidazole-induced encephalopathy in a patient with acute lymphoblastic leukemia during chemotherapy. A 17-year-old girl was admitted to our institution with complaints of abdominal pain and mucoid stools. She was diagnosed with acute lymphoblastic leukemia and had been undergoing intensified chemotherapy protocol. During the fifth week of interim maintenance-1 therapy, she developed a fever and complained of chills. On stool examination, stool occult blood was positive and *Clostridium difficile* toxin A/B test was positive. She was started on metronidazole treatment for possible *Clostridium difficile* infection and other inflammatory gastrointestinal diseases. Ten days later, the patient complained of dizziness and nausea. A brain MRI was performed to make a differential diagnosis of any chemotherapy-induced CNS complication such as necrotizing leukoencephalopathy. The brain MRI showed features of metronidazole-induced encephalopathy. Metronidazole was discontinued and symptoms started to subside four days after. A follow-up brain MRI performed at four weeks showed that lesions of the dentate nucleus had disappeared.

**Key Words:** Metronidazole, Encephalopathy, Chemotherapy, Leukoencephalopathy

**Introduction**

Patients with acute lymphoblastic leukemia (ALL) receiving chemotherapy can develop central nervous toxicity, such as encephalopathy, extrapyramidal disorders, and cerebellar disorders. Some of these disorders are fatal such as necrotizing leukoencephalopathy. Encephalopathy is a condition characterized by altered brain function and it is often the result of a diffuse cerebral disorder. Cerebellar disorders are characterized by dizziness, lack of coordination, imbalance, ataxia, and eye movement impairment. Various factors contribute to neurologic complications including metabolic, hypoxic, nutritional, infectious, and coagulation disorders as well as drugs including chemotherapeutic agents [1,2].

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**References:**

[1] Doe, J. and Smith, M. 2017. Cerebellar disorders and chemotherapy. Clin Pediatr Hematol Oncol 2017;24:153−156

[2] Jane, K. 2016. Metronidazole-induced encephalopathy in pediatric oncology patients. Clin Pediatr Hematol Oncol 2016;23:123−126
Another major side effect of chemotherapy is an increased risk of infection with immunosuppression, resulting in massive antimicrobial usage in chemotherapy patients. Frequent and prolonged antibiotic usage for the treatment of infections, prophylaxis for infection and some chemotherapeutic agents promote the development of *Clostridium difficile* associated diarrhea. Metronidazole is a standard therapy for *Clostridium difficile* with diarrhea [3].

Metronidazole is a 5-nitroimidazole antibiotic with potent activity against anaerobic bacteria and protozoa. While metronidazole is very safe and well tolerated and is commonly prescribed, it can rarely cause serious neurological adverse events, including cerebellar dysfunction, encephalopathy and seizures. While many reports have been presented on liver abscesses in adult patients, few have been presented on pediatric patients or chemotherapy situation [4].

We report our experience regarding metronidazole-induced encephalopathy in a patient with acute lymphoblastic leukemia during chemotherapy and provide a brief review of the related literature.

**Case Report**

A 17-year-old girl was admitted to our institution with complaint of lower abdominal pain and mucoid stool. She had been diagnosed with acute lymphoblastic leukemia and under COG (children’s oncology group)-AALL0232-protocol-based chemotherapy [5]. During the fifth week of interim maintenance-1 therapy, she developed a fever and complained of chills. Significant laboratory findings were WBC 3,900/μL (neutrophils 74%), Hb 8.9 g/dL, platelet 100,000/μL, and CRP 3.39 mg/dL. On stool examination, stool occult blood and CD A/B (*Clostridium difficile* toxin A and B) were positive, but stool culture showed no any organisms. Diarrhea multiplex PCR showed *Clostridium difficile* toxin positive, also. Other laboratory parameters were not remarkable. A computed tomography of her abdomen showed diffuse edematous wall thickening in the rectosigmoid and descending colon, thought to suggest the presence of nonspecific colitis. Radiographic examination revealed no evidence of pancreatitis or ascites. She re-

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**Fig. 1.** Initial MRI on the 10th day of metronidazole treatment. A-B. Axial T2 weighted (A) and FLAIR images (B) demonstrate bilateral symmetric hyperintense lesions in the dentate nuclei of the cerebellum. The contrast enhanced T1 weighted image (C) shows mild enhancement. The lesions of the dentate nuclei of the cerebellum are slightly hyperintense on diffusion weighted image (D).
ceived intravenous metronidazole with 500 mg per 8 hours.

On the fourth day of metronidazole treatment, the chemotherapy of interim maintenance-I day 41 (vincristine, methotrexate, L-asparagenase) was accomplished because laboratory data including hematologic and chemical parameter was available.

On the tenth day of metronidazole treatment, she noted a sudden onset of imbalance, gait disturbance, dizziness, and nausea. There was no weakness, sensory loss or cognitive impairment. A brain magnetic resonance imaging (MRI) with enhancement demonstrated bilateral symmetric hyperintense lesions in the dentate nuclei of the cerebellum (Fig. 1). Following consultation with the radiologist, these findings were felt to be most consistent with metronidazole-induced cerebellar toxicity in view of concomitant metronidazole use and characteristic involvement of dentate nuclei.

Further laboratory evaluation showed WBC 1,620/µL (neutrophils 40%), Hb 8.8 g/dL, platelet 7,800/µL, and CRP 0.20 mg/dL. Stool examination revealed stool occult blood to be negative and CD A/B (Clostridium difficile toxin A and B) was negative, as well. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 119 and 89 IU/L (normal up to 40 IU/L), respectively. Total bilirubin and direct bilirubin were 1.62 mg/dL (normal up to 1.2 mg/dL) and 0.9 mg/dL (normal up to 0.4 mg/dL). All other laboratory findings were normal.

We discontinued methotrexate administration. On the fourth day after the cessation of metronidazole, her dizziness symptoms were improved.

A subsequent MRI was done at four weeks after cessation of metronidazole. The imaging study showed that the lesions of the dentate nucleus have disappeared (Fig. 2). On neurologic examination, all cerebellar signs had resolved.

Discussion

The common use of metronidazole to treat Clostridium difficile infections makes it important to be aware of metronidazole-induced encephalopathy (MIE), a rare complication of metronidazole therapy. The diagnosis of MIE depends on high clinical suspicion based on the drug history, characteristic imaging abnormalities, as well as dramatic im-

![Fig. 2. Follow-up MRI obtained 4 weeks after metronidazole discontinuation. T2 weighted (A) and FLAIR (B) images show that the lesions of the dentate nucleus have disappeared. The contrast enhancement (C) and hyperintensity of the lesion on diffusion weighted image (D) also have disappeared.](image-url)
Characteristic abnormalities in MIE, indicated on MRI, are almost in the form of symmetrical and bilateral T2W or FLAIR hyperintensities with minimal hypointensity on T1W images in the areas of cerebellar dentate nucleus. Other sites include the midbrain, splenium of the corpus callosum, pons, medulla, inferior colliculus, subcortical white matter, basal ganglia and middle cerebellar peduncle. These are the most significant diagnostic clues differentiating MIE from other chemotherapy induced leukoencephalopathy [6,8]. We were able to diagnose our patient by clinical suspicion recognizing the metronidazole medication other than chemotherapy, and radiologic suspicion recognizing the characteristic MRI abnormal intensities.

The mechanism of MIE is not well known. The duration and dose of metronidazole treatment to induce MIE are variable but usually of a long duration or higher doses [7,9]. The pathologic changes in the blood-brain barrier during chemotherapy can enhance the chemotherapy-induced neurotoxicity [1]. Regarding the metronidazole-induced neurotoxicity, Kuriyama et al. [4] reported that the average duration of metronidazole treatment was 54 days (95% CI, 21.2-87.9 days). The average daily dose was 719 mg (range, 250-2,000 mg) and the average cumulative dose of metronidazole was 93.4 g (0.25-1,095 g) [4]. Our patient was administered 1.5 g daily for 10 days, and the cumulative dose was 15 g.

During chemotherapy, our patient was administered with vincristine and high-dose methotrexate during an interim maintenance course. Although her AST and ALT were elevated slightly, her liver dysfunction may be aggravated with the concomitant medication of metronidazole; the clearance rate of metronidazole could thus be reduced and its half-life could be increased, similar to the cases of decompensated cirrhosis and hepatic encephalopathy in patients. The evaluation of MIE is more complicated in patients having underlying liver dysfunction [6,10].

Regarding the prognosis, most abnormal MRI lesions and symptoms show significant improvement or complete resolution within several days to weeks of cessation of metronidazole. However, several reports have shown fatal or irreversible courses [7,9].

In conclusion, as the metronidazole among antimicrobial medications can induce neurotoxicity, the pediatric hematolo-gy-oncologist should have a higher index of suspicion for MIE in managing patients with ALL chemotherapy and neurologic abnormal symptoms, and be aware of the diagnostic significance of MIE to determine whether to discontinue metronidazole or to continue metronidazole and withhold chemotherapy for the neurologic abnormalities.

References

1. Minisini AM, Paulotto G, Andreotta C, Bergonzzi P, Fasola G. Anticancer drugs and central nervous system: clinical issues for patients and physicians. Cancer Lett 2008;267:1-9.
2. Kim KI, Choe BK, Kim HS, Kim JS, Lee HJ. A case of reversible posterior leukoencephalopathy in a child with acute lymphoblastic leukemia. Clin Pediatr Hematol Oncol 2007;14:78-82.
3. Rolston KV. New antimicrobial agents for the treatment of bacterial infections in cancer patients. Hematol Oncol 2009;27:107-14.
4. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. Clin Neuropharmacol 2011;34:241-7.
5. Mattano LA Jr, Devidas M, Winick N, et al. Effects of dexamethasone (DEX) vs prednisone (PDN) and high-dose methotrexate (HD-MTX) vs capizzi methotrexate/asparaginase (C-MTX/ASNase) on osteonecrosis (ON) incidence in children and young adults with high risk acute lymphoblastic leukemia (HR-ALL): A report from the Children’s Oncology Group (COG) Study AALL0232, Blood (54th ASH Annual Meeting) 2012;120:665.
6. Roy U, Panwar A, Pandit A, Das SK, Joshi B. Clinical and neuroradiological spectrum of metronidazole induced encephalopathy: our experience and the review of literature. J Clin Diagn Res 2016;10:0C0E101-9.
7. Hobbs K, Stern-Nezer S, Buckwalter MS, Fischbein N, Finley Caulfield A. Metronidazole-induced encephalopathy: not always a reversible situation, Neurocrit Care 2015;22:429-36.
8. Godfrey MS, Finn A, Zainah H, Dapaah-Afriyie K. Metronidazole-induced encephalopathy after prolonged metronidazole course for treatment of C. difficile colitis, BMJ Case Rep 2015;2015, pii: bcr2014206162.
9. Graves TD, Condon M, Loucaidou M, Perry RJ. Reversible metronidazole-induced cerebellar toxicity in a multiple transplant recipient, J Neurol Sci 2009;285-238-40.
10. Sonthalia N, Pawar SV, Mohite AR, et al. Metronidazole-induced encephalopathy in alcoholic liver disease: a diagnostic and therapeutic challenge, J Emerg Med 2016;51:e79-e83.