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Pediatric B Cell Acute Lymphoblastic Leukemia presenting with Paraneoplastic Acute Disseminated Encephalomyelitis

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Abstract
Acute Disseminated Encephalomyelitis (ADEM) is a monophasic demyelinating disease most often triggered by infection or immunization, though associations with malignancy and stem cell transplant have been described. We described the case of a four-year-old boy with new-onset neurological symptoms associated with ADEM, acute leukemia, and equivocal evidence of Mycoplasma pneumoniae infection. He responded to a short course of antibiotics and chemotherapy for B cell acute lymphoblastic leukemia (B-ALL) that included a prolonged course of high dose steroids with immunosuppressive therapy. This case illustrated a possible association between paraneoplastic ADEM and leukemia in pediatric patients.
Keywords: Encephalomyelitis, Leukemia, Paraneoplastic

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Introduction

Acute Disseminated Encephalomyelitis (ADEM) is an autoimmune demyelinating disease commonly associated with a preceding infection or immunization in children (1). Rarely, ADEM develops as a paraneoplastic complication of malignancy. In adults, paraneoplastic ADEM is associated with lung and ovarian cancer and lymphoma and has been described in children with benign ovarian tumors and lymphomas (2-6). B cell acute lymphoblastic leukemia (B-ALL) is the most common cancer in children. Neurological involvement in acute lymphoblastic leukemia (ALL) occurs due to central nervous system (CNS) infiltration. Affected patients may present with headache, seizures, focal neurological deficits or may be asymptomatic despite the presence of blasts in the cerebrospinal fluid (CSF). We described a patient with newly diagnosed ALL who presented with features of ADEM without evidence of CNS leukemia.

Case Report

A previously healthy four-year-old boy was admitted to the emergency department with new-onset seizures. His first episode was characterized by abnormal staring, loss of muscle tone, urinary incontinence, and left lower extremity weakness. Subsequent episodes were characterized by bilateral lower extremity shaking, facial twitching, and eye deviation with eventual return of baseline neurological function. Family history was remarkable for systemic lupus erythematosus in the mother and maternal grandmother. On initial examination, the patient was noted to be tired but interactive without evidence of focal neurological deficits. He later developed agitation and confusion, suggesting encephalopathy. Laboratory evaluation revealed pancytopenia (Hemoglobin 6.9 g/L, white blood cell

(WBC) 3.9x109/L, absolute neutrophil count (ANC) 0.9 x109/L, platelets 103 x109/L). Elevated transaminases (aspartate transaminase-456 U/L, alanine transaminase-118 U/L), lactate dehydrogenase (1444 U/L), ferritin (2505 ng/mL), reticulocyte % (4.1), and decreased haptoglobin (<12 mg/dL) and glucose-6-phosphate dehydrogenase activity (5.1 U/g Hgb) were also observed. Uric acid, triglycerides, coagulation factors, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were normal. Head computed tomography (CT) and electroencephalogram (EEG) were unremarkable. Brain magnetic resonance imaging (MRI) revealed multiple bilateral fluid attenuated inversion recovery (FLAIR) and T2 hyper-intense foci predominantly in white matter suggestive of ADEM (Fig. 1). Cerebrospinal fluid (CSF) studies showed elevated protein (93.1 mg/dL), albumin (51.4 mg/dl, N=13-27) and CSF immunoglobulin G (IgG) (13.7 mg/dl, N=0.5-8.1) with normal cells (3 WBCs and 1 red blood cell (RBC)). CSF gram stain, cultures, and polymerase chain reaction (PCR) meningitis panel were negative. MRI of the spine revealed abnormal marrow signal as well as a non-operative complex epidural fluid collection from T2 to T10 (Fig. 2). Autoimmune evaluation, including CSF paraneoplastic and encephalopathy autoimmune panel and anti-myelin oligodendrocyte glycoprotein (MOG) antibody returned negative. Antinuclear Antibody (ANA) titers revealed low level anti-scleroderma antibodies (1.7 AU/ml). The patient had positive IgM serology for Mycoplasma pneumoniae. Blood culture, respiratory PCR, Sars CoV2 PCR was negative. The patient started Levetiracetam for seizures and completed a seven-day course of Doxycycline for possible active Mycoplasma pneumoniae infection. After peripheral blood flowcytometry suggestion about the presence of abnormal immature B cells, a bone marrow biopsy was performed, which revealed 75% B lymphoblasts, confirming a diagnosis of B-ALL. Multi-agent chemotherapy with high dose oral steroids was administered per Children's Oncology Group study protocol (AALL 1731) (7). While somnolent and irritable for the first 48-72 hours of hospitalization, the patient returned to his neurological baseline prior to starting chemotherapy. CSF protein normalized within a week of treatment. Repeated neuroimaging showed improved white matter hyper-intensities in the brain and resolution of the epidural fluid collection in the spine. He continued to show sustained improvement and is now one year on treatment.

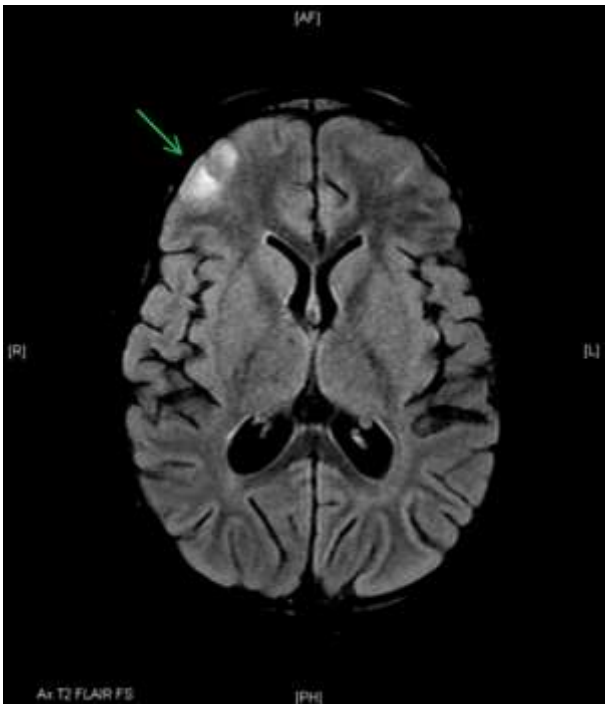

Figure 1: Axial T2 FLAIR imaging revealing foci of increased signal intensity in right frontal subcortical white matter that resolved after chemotherapy

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Figure 2: Sagittal T2 imaging revealing complex fluid collection in the dorsal epidural space of the thoracic spine as well as abnormal marrow signal and enhancement of the vertebral bodies.

Discussion

This atypical presentation of ALL with seizures and abnormal neuro-imaging findings in the absence of CNS leukemia suggests the possibility of ADEM as a paraneoplastic syndrome associated with pediatric B-ALL, which, though rare, has been reported in the literature (8,9). Response to chemotherapy helps support this diagnosis.The patient`s presenting symptom was seizure and neuroimaging revealed multifocal lesions in the white matter suggestive of ADEM. ADEM is a monophasic demyelinating disease of the CNS characterized by typical neuroimaging findings coupled with clinical symptoms including seizures and altered mental status (1). Associated findings are elevated protein without CSF pleocytosis. ADEM is linked with infectious or autoimmune triggers, though in many cases, no etiological factor is identified (1). Our patient had a positive qualitative serologic test for Mycoplasma pneumoniae, which has a high false positive rate due to seroprevalence of the infection in this age group (10,11). Concomitant or follow-up CSF testing by culture or PCR might have helped establish a more definitive diagnosis, but a negative result would not rule out the possibility of autoimmune-mediated ADEM triggered by Mycoplasma pneumoniae infection, a known association. Neurological involvement in B-ALL is characterized by presence of blasts in the CSF or mass lesions in neuroimaging. Neither of these were present in our case. The neuroimaging findings of white matter hyper-intensities and elevated CSF protein, albumin, and IgG levels thus make ADEM the most likely diagnosis. The absence of a definitive infectious etiology coupled with a known diagnosis of B-ALL made us hypothesize that in this case, ADEM could be a paraneoplastic syndrome. The clinical variation in neurological paraneoplastic syndromes is related to an aberrant antibody interaction with neuronal proteins in response to cancer antigens (12,13). They are common in adult solid tumors such as lung and ovarian cancers or hematologic malignancies such as lymphoma (2,3). Despite known pediatric associations like opsoclonus-myoclonus syndrome and neuroblastoma (6) their association with childhood leukemia is very rare; an expanded literature search yielded only two cases (8,9). In the first report, the patient presented with seizures, altered sensorium and neuroimaging was suggestive of ADEM; response was seen with steroids and chemotherapy, however, the patient succumbed to infectious complications (8). In the second case, the diagnosis of leukemia was made a month after the initial diagnosis of ADEM, the features of which resolved with intravenous immunoglobulin (IVIG) before recurrence a month later; once leukemia was diagnosed and specific treatment initiated, the ADEM lesions resolved (9). Additionally, this patient was encephalopathic prior to chemotherapy, so the authors postponed day 1 intrathecal chemotherapy and substituted

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Methotrexate with Hydrocortisone/ Cytarabine due to concern of worsening symptoms. Our patient tolerated intrathecal chemotherapy well and did not need any chemotherapy modifications. An initial diagnosis of consideration for this patient was post-infectious ADEM. The pancytopenia could be consistent with transient bone marrow suppression and the elevated lactate dehydrogenase (LDH) and anemia could be attributed to hemolysis in a patient with Glucose-6 phosphate dehydrogenase (G6PD) deficiency. However, peripheral flow cytometry results suggested an alternative diagnosis.

An additional unique feature of our patient is the epidural fluid collection associated with leukemic infiltration of the vertebral bodies visible on MRI of the spine. This collection was felt to be likely related to the patient's leukemia or associated paraneoplastic disease, as it resolved with chemotherapy. While CSF paraneoplastic and encephalopathy panel returned negative, this does not exclude paraneoplastic ADEM (14). Though ADEM is a well-described paraneoplastic syndrome in adult cancer, this case illustrated the rare association of ADEM as a presenting feature of B-ALL in children and emphasized the consideration of malignancy in a child presenting with pancytopenia and encephalitis.

Conclusion

He responded to a short course of antibiotics and chemotherapy for B cell acute lymphoblastic leukemia (B-ALL) that included a prolonged course of high dose steroids with immunosuppressive therapy. This case illustrated a possible association between paraneoplastic ADEM and leukemia in pediatric patients.

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Conflict of interest

The authors had no conflict of interest to declare.

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