Pediatric Neurology 57 (2016) 91–94

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Fatal Central Nervous System Disease Following First Infliximab Infusion in a Child With Inflammatory Bowel Disease

Fiona M. Baumer MD [a,*,1], Jodie Ouahed MD, MMSc [b,c,1], Menno Verhave MD [b,c], Michael J. Rivkin MD [a,d,e]

[a] *Department of Neurology, Boston Children's Hospital, Boston, Massachusetts*
[b] *Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Boston Children's Hospital, Boston, Massachusetts*
[c] *Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts*
[d] *Department of Psychiatry, Boston Children's Hospital, Boston, Massachusetts*
[e] *Department of Radiology, Boston Children's Hospital, Boston, Massachusetts*

ABSTRACT

BACKGROUND: Infliximab is used in the treatment of inflammatory bowel disease. Previously reported neurological complications include central and peripheral demyelinating disorders and neuropathies occurring months into therapy. **PATIENT DESCRIPTION:** A seven-year-old boy diagnosed with ulcerative colitis and primary sclerosing cholangitis received infliximab. Six hours following his uneventful infusion, he awoke with headache and emesis and rapidly became obtunded. Neurological examination revealed minimally reactive pupils and otherwise absent brainstem reflexes. Cranial computed tomography revealed hypodense lesions in the cerebral hemispheres, cerebellum, and pons accompanied by hemorrhage. Magnetic resonance imaging showed diffusion restriction concerning for ischemia with areas of ring enhancement suggestive of inflammation. Vessel imaging was normal, and cerebrospinal fluid and serum studies showed only an extremely elevated level of d-dimer. Echocardiogram showed depressed ventricular function but neither intracardiac shunt nor thrombus. Within four days he met criteria for brain death. Autopsy was refused. **CONCLUSIONS:** This is the first report of a fulminant, fatal central nervous system process to occur after an initial dose of infliximab. The differential diagnosis includes multifocal arterial strokes and a devastating demyelinating process.

Keywords: ulcerative colitis, primary sclerosing cholangitis, inflammatory bowel disease, infliximab, ischemic stroke, demyelinating disease, acute hemorrhagic leukoencephalitis, AHLE

Pediatr Neurol 2016; 57: 91-94

Introduction

Infliximab, a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α), can be used to treat Crohn disease and ulcerative colitis (UC). Established severe side effects include infusion reactions, hematologic abnormalities, infections, hepatotoxicity, and increased risk of malignancy and lymphoma. Neurological complications are rare and include central and peripheral demyelinating diseases and neuropathies that usually occur months following treatment.[1]

Patient Description

This previously healthy boy presented with bloody diarrhea, abdominal pain, emesis, and elevated levels of liver enzymes and was diagnosed with UC and primary sclerosing cholangitis at age 6.5 years. He had no family history of inflammatory bowel diseases (IBD). Despite a good response to early courses of prednisone, he experienced recurrent colitis on sulfasalazine monotherapy, at which point treatment with 6-

Disclosures: The authors have nothing to disclose.
Author Contributions: Each author was closely involved in the clinical care of the patient described. Each author participated in preparing the manuscript, its intellectual content, and critical revisions and edits.
Funding Sources: None to disclose.
Article History:
Received September 9, 2015; Accepted in final form December 20, 2015
* Communications should be addressed to: Dr. Baumer; Lucile Packard Children's Hospital; Stanford Division of Child Neurology; 730 Welch Rd #2; Palo Alto, CA 94304.
E-mail address: fbaumer@stanford.edu
[1]Authors contributed equally to this work.

0887-8994/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.12.017

mercaptopurine (6-MP) was initiated. Three months later, he demonstrated persistent anemia with hemoglobin of 8.5 mg/dL, so his dose of 6-MP was increased. Two months thereafter, 6-MP levels were undetectable and he manifested worsened anemia (hemoglobin 7.6 mg/dL). A planned flexible sigmoidoscopy to reassess disease severity before initiating infliximab was delayed by family-related complications. Ultimately, despite optimized treatment with 6-MP, supplemental iron, and sulfasalazine, he demonstrated tachycardia, marked anemia (hemoglobin of 6.2 mg/dL) and hematochezia. He was admitted for stabilization, blood transfusion, expedited colonoscopy, and initiation of infliximab. He was treated with oral vancomycin when stool was positive for *Clostridium difficile*. Upper endoscopy and colonoscopy revealed chronic mildly active pancolitis.

The first dose of infliximab was associated with a transient sinus arrhythmia. Electrocardiogram revealed a normalized rhythm, so he was discharged that evening. Six hours following completion of the infusion, he awoke from sleep with severe headache and dizziness. Initially he was able to speak and walk, but 30 minutes later he vomited and became unresponsive. Evaluation at an outside hospital revealed that he was dusky, comatose, tachycardic, and hypotensive, with agonal respirations and unreadable oxygen saturations. He was intubated and treated empirically for anaphylactic and septic shock before transfer to our hospital.

Upon arrival he remained unresponsive and unsedated. His examination revealed a minimally reactive right pupil but otherwise brainstem reflexes were absent. He had flaccid paralysis and areflexia of the lower but not upper extremities. An emergency cranial computed tomography scan showed multifocal hypodense lesions with surrounding edema involving both hemispheres and the brainstem. The left-sided lesions were the largest, and a left occipital lesion included hemorrhage. He was empirically treated for increased intracranial pressure (ICP) with hypertonic saline and mannitol, but after an external ventricular drain was placed, ICP was found to be normal. Subsequent magnetic resonance imaging with magnetic resonance angiography revealed T2-weighted signal changes in the cerebral and cerebellar hemispheres bilaterally (Fig 1), left greater than right, as well as the pons with accompanying diffusion restriction. Areas of multifocal hemorrhage affected the entire pons and both cerebral hemispheres, and ring enhancement was noted in the cerebellum and pons. The large vessels appeared normal on magnetic resonance angiography and venography (Fig 2). These findings were most concerning for multifocal ischemic infarcts accompanied by hemorrhage, but a fulminant demyelinating process was also on the differential.

Further evaluation revealed slight leukopenia (leukocytes $3.04x10^{-3}$ cells/μL), an international normalized ratio of 1.4, and a C-reactive protein level of 1.35 mg/dL with a normal erythrocyte sedimentation rate. The cerebrospinal fluid was grossly bloody, with no white blood cells, a normal protein level (26.9 mg/dL), and an elevated level of glucose (158 mg/dL). Cerebrospinal fluid cultures were negative as were polymerase chain reactions for the following infections: cytomegalovirus, Epstein-Barr virus, human herpes virus 6 and 7, mycoplasma pneumonia, and varicella-zoster virus. A hypercoagulability evaluation showed a markedly elevated level of d-dimer, but was otherwise unremarkable for lupus anticoagulant, anti-beta-2-glycoprotein, anticardiolipin antibodies, serum lipoprotein(a), anti-thrombin III, functional assays for proteins C and S, factor V Leiden, serum homocysteine, von Willebrand factor antigen, and prothrombin 20210 mutation. Echocardiography revealed mild right ventricular hypertension and severe global left

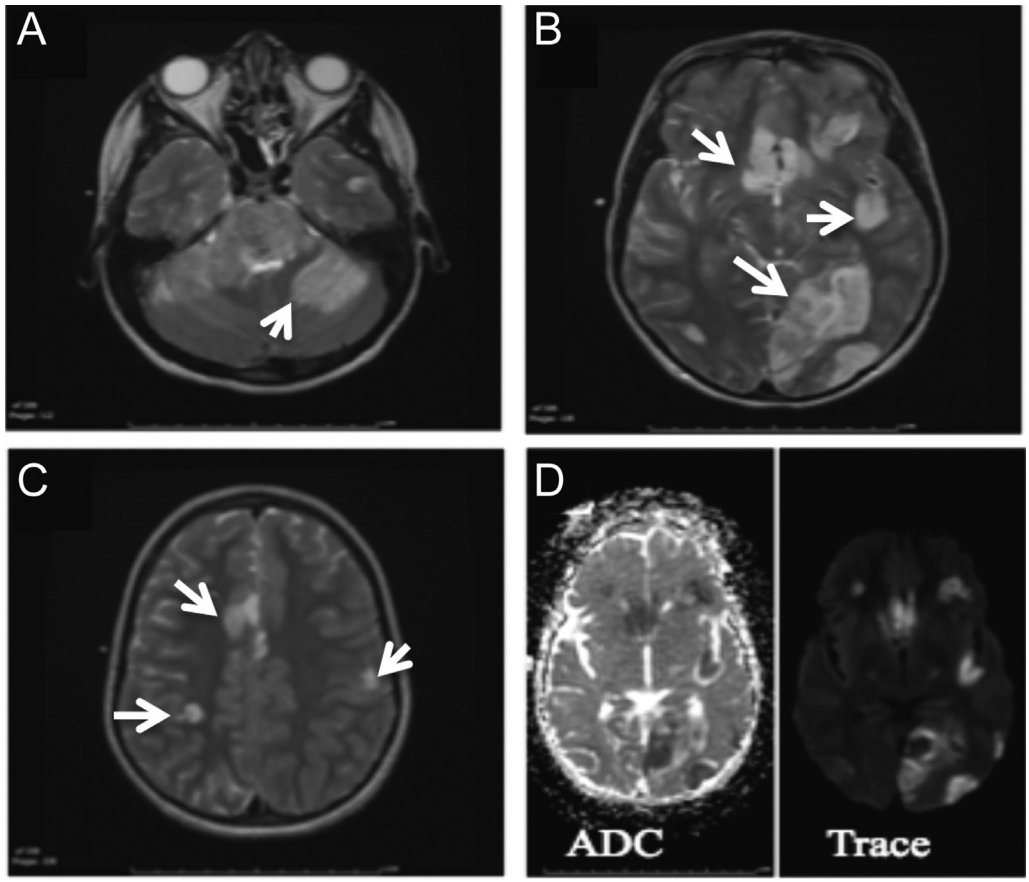

FIGURE 1.
Magnetic resonance imaging of the brain fluid-attenuated inversion recovery images (A-C): Axial fluid-attenuated inversion recovery sequences illustrating the extent of signal change throughout the posterior fossa and bilateral cerebral hemispheres (indicated by arrows). Diffusion imaging (D): corresponding diffusion restriction in all of these lesions, illustrated at the level of the cerebral hemispheres (dark regions on ADC and bright regions on Trace). ADC = apparent diffusion coefficient.