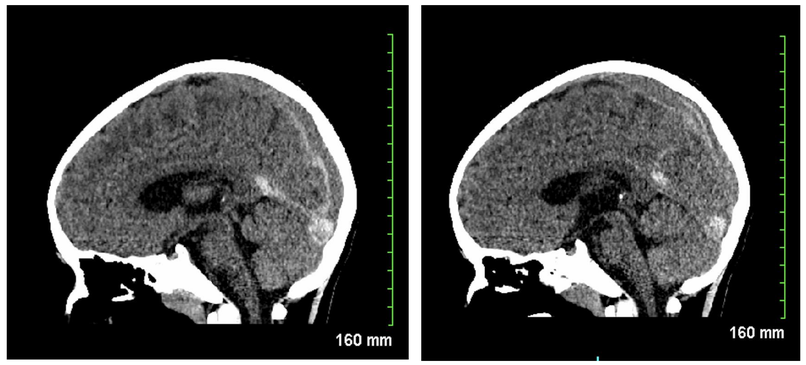
Severe Thromboembolic Events in Two Pediatric Patients Diagnosed with Ulcerative Colitis (UC) and Recently Initiated Adalimumab Therapy: A case series

Kelly Powell, MD; Shreya Patel, DO; Megan Tate, MD; Abby Alaine Unger, BS; Abigail Haythorn,BS
Department of Pediatrics

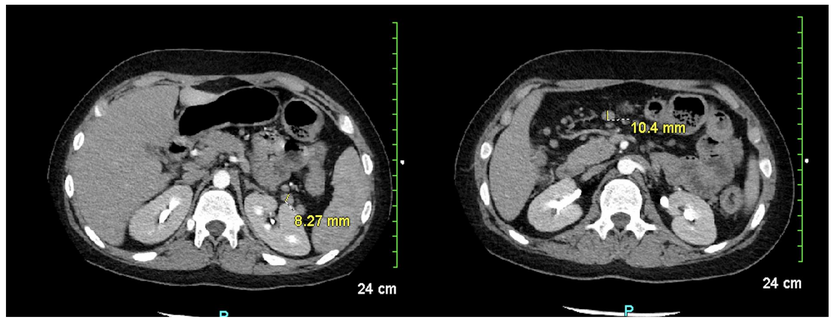
Background

- Inflammatory bowel disease (IBD) is becoming much more prominent in the pediatric population with patients being diagnosed now at very young ages. Ulcerative Colitis (UC) in particular involves inflammation of the mucosal layers of the colon. Adalimumab is a human monoclonal antibody that disrupts tumor necrosis factor-alpha (TNF-alpha) receptor sites by binding to TNF-alpha and reducing the inflammatory response. It is currently one of the first-line therapies in the treatment of inflammatory bowel disease and has been well studied and approved in the pediatric population.

Imaging



- **Figures 1 and 2**- *Standard and hyperdense transverse sinuses (Right greater than left), hyperdense straight sinus and regions of hyper-density within the posterior inferior superior sagittal sinus concerning for thrombosis.*



- **Figures 3 and 4-** *Multiple bilateral segmental lower lobe pulmonary emboli*

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Case Details

- The first case we present is that of a 4-year-old African American male with known diagnoses of Autism and Ulcerative colitis (~10 months prior).
- Patient had delayed initiation of adalimumab due to parental hesitation and had started on sulfasalazine in the interim. He had received his first dose 2 weeks prior to presentation and his second the day prior to admission.
- Day of admission, mother reported that the patient had suddenly grabbed his head as if he had a headache and then “stared off” before becoming unresponsive.
- In the ED, he had generalized seizure activity that responded to Lorazepam, after which he remained somnolent and post-ictal for several hours. Head CT ultimately showed “hyper-density within the transverse and sagittal sinuses” (**Figures 1 and 2**) concerning for thrombosis, confirmed later with MRI and MRV studies.

- The second case involves a 15-year-old Caucasian male who had been diagnosed with Ulcerative Colitis approximately one month prior to admission, at which time he had significant rectal bleeding and iron deficiency anemia that required multiple pRBC transfusions.
- He, too, received his first injection of adalimumab two weeks prior to presentation, after being bridged on high-dose steroids for two weeks.
- His initial symptoms included a week of left calf pain and swelling that progressively worsened until night prior to admission when he started experiencing left sided pleuritic chest pain and exertional dyspnea.
- Upon arrival to the ED, he was tachycardic with heart rate 136, but vitals otherwise appropriate with respiratory rate 22, blood pressure 104/72, and oxygen saturation 99% on room air.
- He had an US doppler of the left lower extremity that showed DVTs and a CTA chest (**Figures 3 and 4**) that showed bilateral pulmonary emboli.

- Both patients were immediately transferred to the Pediatric ICU and started on heparin infusions until they could be transitioned to subcutaneous anticoagulant therapy.
- Our first patient was subsequently transferred to a different facility for a second opinion
- The second patient has since been admitted multiple times for significant anemia secondary to rectal bleeding. His anticoagulation therapy was subsequently discontinued despite residual segmental emboli in the right lung.

Discussion

Adalimumab and other biologics have been studied and approved for the management of UC in the pediatric population with good outcomes and minimal side effects[3,4]. The coincidental timing of both cases initially led us to believe that the adalimumab was at fault for inciting these thromboembolisms, as there have been studies in adult populations that indicate a possible correlation. Evidence has been shown that antibodies directed toward adalimumab has shown decreased serum concentrations and overall decreased effectiveness of the medication[7]. One possible explanation states that anti-TNF therapy has been associated with induction of autoantibodies, including antinuclear antibodies (ANA) and double-strand (ds) DNA antibodies[8]. However, after further research this seems less likely the scenario as the antibody development requires exposure over time, and these patients had only received therapy for 2 weeks.

UC alone has a nearly 3-fold increase in risk for the development of embolisms[1,2,5], and admission to the hospital makes that risk even higher[6]. The risk of developing thromboembolism is multifactorial and can be derived from the pro-inflammatory state of an acute UC flare. Although, some argue that the risk of VTE is still high while in remission[11]. Additionally, the younger the patient at first VTE occurrence, the more likely there is for recurrence[11]. Currently there are not many pediatric studies investigating thromboprophylaxis in the UC population, but further investigation may be warranted in order to better serve this group and improve overall outcomes. What has been studied does indicate that therapeutic heparin is safe[4]. It has also been documented in one specific study that thromboprophylaxis during IBD-associated hospitalization will have a lower risk for developing VTE after discharge. Ultimately, we found several studies that recommended starting anticoagulant prophylaxis in patients with severe UC, especially those currently hospitalized [2,6,9,10].

References

1. Grainge, M.J., West, J., & Card, T.R. (2010). Venous thromboembolism during active disease and remission in inflammatory bowel disease: A cohort study. *The Lancet*, *375*(9715), 657-663.
2. Kohoutova, D., Moravkova, P., Kruzliak, P., & Bures, J. (2014). Thromboembolic complications in inflammatory bowel disease. *Journal of Thrombosis and Thrombolysis. 39*(4), 489-498.
3. Choi, S. Y., & Kang, B. (2022). Adalimumab in pediatric inflammatory bowel disease. *Frontiers in Pediatrics*, *10*.
4. Aloi, M., Bramuzzo, M., Arrigo, S., Romano, C., D'Arcangelo, G., Lacorte, D., Gatti, S., Illiceto, M. T., Zucconi, F., Dilillo, D., Zuin, G., Knafelz, D., Ravelli, A., Cucchiara, S., & Alvisi, P. (2018). Efficacy and safety of Adalimumab in pediatric ulcerative colitis: A real-life experience from the Sigenp-IBD Registry. *Journal of Pediatric Gastroenterology & Nutrition*, *66*(6), 920–925.
5. Zhang, X.-Y., Dong, H.-C., Wang, W.-F., & Zhang, Y. (2022). Risk of venous thromboembolism in children and adolescents with inflammatory bowel disease: A systematic review and meta-analysis. *World Journal of Gastroenterology*, *28*(16), 1705–1717.
6. Aardoom, M. A., Klomberg, R. C., Kemos, P., Ruemmele, F. M., Fagbemi, A., Kiparissi, F., Schweizer, J. J., Sebastian, S., Russell, R. K., Torrente, F., van Mill, M., de Ridder, L., Croft, N. M., Tempia-Caliera, M., Seah Lee, W., Pigott, A. J., Classen, M., Morris, M.-A., Muhammed, R., … Bigot, L. (2021). The incidence and characteristics of venous thromboembolisms in paediatric-onset inflammatory bowel disease: A prospective international cohort study based on the PIBD-Setquality Safety Registry. *Journal of Crohn's and Colitis*, *16*(5), 695–707.
7. Hindryckx, P., Novak, G., Vande Casteele, N., Khanna, R., Laukens, D., Vipul, J., & Feagan, B. G. (2017). Incidence, prevention and management of anti-drug antibodies against therapeutic antibodies in inflammatory bowel disease: A practical overview. *Drugs*, *77*(4), 363–377.
8. Beigel, F., Schnitzler, F., Paul Laubender, R., Pfennig, S., Weidinger, M., Göke, B., Seiderer, J., Ochsenkühn, T., & Brand, S. (2010). Formation of antinuclear and double-strand DNA antibodies and frequency of lupus-like syndrome in anti-TNF-α antibody-treated patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, *17*(1), 91–98.
9. Zitomersky, N. L., Levine, A. E., Atkinson, B. J., Harney, K. M., Verhave, M., Bousvaros, A., Lightdale, J. R., & Trenor, C. C. (2013). Risk factors, morbidity, and treatment of thrombosis in children and young adults with active inflammatory bowel disease. *Journal of Pediatric Gastroenterology & Nutrition*, *57*(3), 343–347.
10. Lv, X., Gao, X., Liu, J., Deng, Y., Nie, Q., Fan, X., Ye, Z., Liu, P., & Wen, J. (2022). Immune-mediated inflammatory diseases and risk of venous thromboembolism: A mendelian randomization study. *Frontiers in Immunology*, *13*.
11. Giannotta, M., Tapete, G., Emmi, G., Silvestri, E., & Milla, M. (2015). Thrombosis in inflammatory bowel diseases: What's The link? *Thrombosis Journal*, *13*(1).