Autoimmune Overload: An atypical presentation of granulomatosis with polyangiitis in an adolescent with type-1 diabetes mellitus

Jamie Wardinger[1], Lauren Sussman[1], Breann Litwa[2], Elizabeth Irish[2], Llewellyn Foulke[1], and Robert Kaslovsky[2]

[1]Albany Medical Center
[2]Albany Medical College

July 31, 2021

Abstract

We report a case of granulomatosis with polyangiitis (GPA) in a pediatric patient with a history of type 1 diabetes mellitus (T1DM) after a somewhat unusual presentation. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a relatively rare entity in the general population, and are even less common amongst the pediatric population. Our patient's chronic history of vague and systemic symptoms paired with social and environmental stressors contributed to her convoluted picture and late diagnosis. In addition, her T1DM adds an interesting element to her case, begging the question of whether her propensity for autoimmune conditions played a role in the development of this disease. With this case, we hope to increase clinician level of suspicion and promote early diagnosis and treatment for future pediatric patients.

To the Editor,

We present the case of an 11-year-old female with a history of type 1 diabetes, hematochezia, and iron deficiency anemia who was admitted for hypoxia following an endoscopy and colonoscopy. Room air saturations were 80-85%, and she was started on oxygen by nasal cannula. A chest radiograph (Figure 1a) demonstrated findings consistent with viral airway disease, and on nasal swab she was positive for rhino/enterovirus, but negative for COVID.

Further history from her grandmother, her primary caregiver, revealed that the patient had lost weight over the past month, attributed to poor appetite, with nausea, vomiting, and abdominal pain. The patient also exhibited shortness of breath and increased work of breathing with exertion over the past few months, but had no previous history of asthma or lung disease. She had previously been anemic requiring transfusion two months prior for a hemoglobin of 6 g/dL. On admission her hemoglobin was 10.7g/dL.

On the third hospital day, the patient's oxygen requirement increased, prompting transfer to the pediatric intensive care unit (PICU). The patient then developed intermittent hemoptysis, which could be quantified at about a mouthful, warranting a chest computerized tomography scan (CT), (Figure 1b) which was consistent with viral infection or possible pulmonary hemorrhage. Flexible bronchoscopy was performed, where saline lavage resulted in return of frank blood, indicating the presence of pulmonary hemorrhage. Laboratory studies are displayed in Table 1, most notable for elevated antineutrophil cytoplasmic antibody (c-ANCA) of 1280. A lung biopsy was subsequently performed which demonstrated signs of capillaritis with the presence of many inflammatory cells, consistent with vasculitis, while immunofluorescence was pauci immune.

Diagnosis of pediatric granulomatosis with polyangiitis (GPA) requires three of the six following criteria: positive histopathology findings, upper airway involvement, laryngo-trachea-bronchial stenosis, pulmonary involvement, positivity by immunofluorescence or enzyme-linked immunosorbent assay (ELISA), or renal

involvement, with biopsy remaining the gold standard.[1] At this point, the patient now met three of six criteria for GPA, (positive histopathology on biopsy, pulmonary involvement, and positive ANCA) confirming that her hypoxemia and hemorrhage were secondary to pulmonary involvement of GPA. Rituximab and pulse doses of methylprednisolone were initiated, with subsequent clinical improvement. Laboratory studies demonstrated a reduction of her c-ANCA to 320 three weeks after initiation of therapy. She was discharged home with a final diagnosis of c-ANCA positive GPA with primary pulmonary involvement.

At follow up, pulmonary function testing (PFTs) showed forced vital capacity (FVC) 67%, forced expiratory volume (FEV1) 71% and FEV1/FVC ratio of 94%. At subsequent follow-up visits, she was noted to have new-onset epistaxis with nasal septum perforation, meeting a fourth criterion for GPA. She had received two doses of rituximab and was started on Azathioprine, with a taper off prednisone over two months. Eventually she no longer required supplemental oxygen, and her exercise tolerance returned to normal. Her vital capacity improved to 85% predicted and repeat chest CT scan showed significant improvement in the interstitial disease pattern.

GPA is a type of ANCA-associated vasculitis (AAV) that affects the capillaries, venules, and arterioles, most frequently exhibiting c-ANCA/PR3-ANCA (proteinase 3) positivity.[2] The etiology of GPA has yet to be discovered; however, genetic and environmental factors in combination with abnormalities in the innate and adaptive immune system are thought to contribute to the disease process.[3] Clinically, GPA tends to involve the upper respiratory tract, lower respiratory tract, and the renal system(s); however, limited forms of the disease may occur and be confined to a single organ.[4] GPA in childhood tends to be more severe compared to adult-onset with early, aggressive ear-nose-throat (ENT) involvement (subglottic stenosis, nasal septal perforation). A frequent presenting clinical manifestation of childhood GPA is pulmonary involvement, demonstrated by shortness of breath, chronic cough, or hemoptysis secondary to alveolar hemorrhage.[5]

Vasculitides, especially small artery vasculitis, are rare in the pediatric population. The estimated prevalence of children with ANCA-associated vasculitis is 3.41-4.28 per million children, with a higher female predominance.[3,4] Therefore, GPA was not suspected for this young patient. It was only when all symptoms were put together did a GPA diagnosis become clear.

In our patient, the late diagnosis was likely due to the individual systemic presentations that were not obvious for vasculitis. Looking back at the complete history, she presented with iron deficiency anemia, shortness of breath, abdominal pain with subsequent hypoxia, and hemoptysis. The dyspnea and abdominal pain were initially attributed to anxiety caused by her complex social history, which included incarcerated parents and transfer of care from the aunt to the grandmother. In retrospect, the iron deficiency anemia, while treated initially as an isolated event, was likely due to ongoing pulmonary hemorrhage. Notably, pediatric patients usually present with suspicion for GPA when in renal failure, however, our patient had consistently normal kidney function. At what point in this constellation of symptoms would a clinician have reasonably suspected GPA? The answer could easily be never.

Another unique presentation of this patient was that she had a previous diagnosis of Type 1 Diabetes (T1DM) and was later diagnosed with a second autoimmune disorder, GPA. Comorbidities with multiple autoimmune disorders are relatively common, however the research does not show GPA as a known concurrent diagnosis. Was this patient an anomaly, or was she more prone to GPA because of her existing T1DM? Given the little information available, either is a possibility. It also brings into question the management. Guidelines for GPA indicate that induction therapy to achieve remission includes rituximab and prolonged use of corticosteroids.[3] In our patient, who has T1DM, it questions whether this course of treatment was ideal. Overall, it shows that management of dual autoimmune disorders affected by individual treatment methods may need to be modified in future.

In summary, the incidence of childhood-onset GPA is exceedingly rare, occurring in only 0.02 to 0.64 per 100,000 children per year, and is nearly undocumented in the T1DM population.[4] It is not clearly understood whether this patient had a propensity toward autoimmune diseases which increased her likelihood of developing GPA while also having T1DM or if this combination is unrelated and completely coinciden-

tal. Her history of present illness, including the preceding months of various symptoms, led ultimately to a predominantly pulmonary picture of dyspnea, hypoxia, and hemoptysis on initial presentation without any renal involvement, unlike typical GPA.[6] For these reasons, one would need to have high suspicion to include GPA in the differential diagnosis and workup of a pediatric patient with hemoptysis. Recognizing and diagnosing childhood GPA in a timely manner poses many challenges, as many pediatric cases do not present with enough clinical features at one time to suspect the diagnosis, leading to delayed or even missed diagnosis. One must have high clinical suspicion so that appropriate treatment may be initiated.

References:

1. Calatroni M, Oliva E, Gianfreda D, et al. ANCA-associated vasculitis in childhood: recent

advances. Ital J Pediatr. 2017;43(1):46.

https://doi:10.1186/s13052-017-0364-x

2. Cabral DA, Canter DL, Muscal E, et al. Comparing Presenting Clinical Features in 48 Children with

Microscopic Polyangiitis to 183 Children Who Have Granulomatosis with Polyangiitis

(Wegener's): An ARChiVe Cohort Study. Arthritis Rheumatol. 2016;68(10):2514-2526.

https://doi.org/10.1002/art.39729

3. Jariwala M, Laxer RM. Childhood GPA, EGPA, and MPA. Clin Immunol 2020; 211:108325.

https://doi:10.1016/j.clim.2019.108325

4. Hirano D, Ishikawa T, Inaba A, et al. Epidemiology and clinical features of childhood-onset antineutrophil cytoplasmic antibody-associated vasculitis: a clinicopathological analysis. Pediatr

Nephrol. 2019;34(8):1425-1433.

https://doi:10.1007/s00467-019-04228-4

5. Filocamo G, Torreggiani S, Agostoni C, Esposito S. Lung involvement in childhood onset

granulomatosis with polyangiitis. Pediatr Rheumatol Online J. 2017;15(1):28.

https://doi:10.1186/s12969-017-0150-8

6. Ludici M, Quartier P, Terrier B, Mouthon L, Guillevin L, Puéchal X. Childhood-onset

granulomatosis with polyangiitis and microscopic polyangiitis: systematic review and metaanalysis. Orphanet J Rare Dis. 2016;22;11(1):141.

https//: doi:10.1186/s13023-016-0523-y

Hosted file

`GPA case report TABLE 1.docx` available at https://authorea.com/users/428518/articles/532339-autoimmune-overload-an-atypical-presentation-of-granulomatosis-with-polyangiitis-in-an-adolescent-with-type-1-diabetes-mellitus