Limited GPA and Alpha-1 Antitrypsin Deficiency in a Pediatric Patient

To the Editor:

Granulomatosis with polyangiitis (GPA) is a rare systemic vasculitis affecting small to medium-sized blood vessels. The most frequent presenting symptoms are nonspecific constitutional symptoms, followed by pulmonary, renal, and upper respiratory tract symptoms[1]. Alpha-1-antitrypsin (A1AT) deficiency is the most common genetic cause of liver disease in children[2]. We present a case of concurrent GPA and A1AT deficiency in a pediatric patient. Consent for this case report was obtained from the patient's family. Because this is a case report, a waiver from ethics review was granted by the Hamilton Integrated Research Ethics Board.

A previously healthy 3-year-old female was referred to pediatric rheumatology for subglottic stenosis. She had presented numerous times to the emergency department over several months with recurrent episodes of cough, nasal congestion, shortness of breath, and stridor. Oral dexamethasone produced dramatic symptomatic improvement. Unfortunately, she experienced ongoing congestion and stridor between steroid courses.

History of presenting illness was negative for rash, joint pain/swelling, hematuria, or constitutional symptoms. Past medical history was unremarkable. Family history was positive for childhood asthma in her mother, and systemic lupus erythematosus in her maternal grandmother. Physical examination was unremarkable. However, laryngoscopy during one of her ENT visits revealed grade I subglottic stenosis with erythema.

Laboratory investigations showed elevated erythrocyte sedimentation rate (ESR; 50 mm/h) and C-reactive protein (CRP; 26 mg/l). Serological examination, by ELISA, for anti-myeloperoxidase was mildly elevated at 3.5 AI (normal < 1.0 AI), and negative for antinuclear antibody and anti-proteinase 3. Her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated at 40 u/l (normal 18–36 u/l) and 50 u/l (normal < 26 u/l), respectively. Complete blood count was normal, with white blood cells 7.7×10^9 cells/l, Hb 126 g/l, and platelets 513×10^9/l. Urinalysis was normal. Infectious investigation was negative for fungi and mycobacterium. Computed tomography scan of the chest and sinuses revealed bilateral lung atelectasis, grade II subglottic stenosis, and pansinusitis. Sinus biopsy showed evidence of necrotizing granulomas with many multinucleated giant cells and very dense mixed inflammatory infiltrate, in keeping with GPA.

The patient had no other systemic symptoms regarding pulmonary or renal systems, and she was diagnosed with limited GPA according to European Vasculitis Society/European League Against Rheumatism staging[3]. Treatment with oral prednisone at 1 mg/kg/day with slow taper and subcutaneous methotrexate (MTX) was initiated. The patient responded well, experiencing no further stridor or nasal congestion. One month after initiating treatment, her ESR and CRP normalized.

Followup bloodwork showed persistently elevated liver enzymes. Investigations for causes of chronic hepatitis revealed a low serum A1AT level of 0.33 g/l (normal 0.88–1.7 g/l). Genetic testing identified the A1AT PI*ZZ phenotype, reflecting the most severe presentation of A1AT deficiency. Both parents were found to be carriers of A1AT (PI*MZ) deficiency.

We decided that her persistent mild transaminitis was due to both the A1AT deficiency and MTX therapy. She was therefore transitioned from MTX to mycophenolate mofetil. The patient's most recent bloodwork demonstrates persistent mild transaminitis, with ALT 39 u/l but normal AST (35 u/l). Her ESR and CRP remain normal. She is clinically inactive with no stridor and no signs of decompensated liver disease.

Subglottic stenosis is a manifestation of GPA that can occur independently of systemic manifestations[4,5]. It occurs more frequently in children than in adults. For this reason, the 2010 diagnostic criteria for pediatric GPA includes sinus inflammation and laryngotracheobronchial involvement, which were not in the original criteria for adult GPA[3]. Disease stages of GPA have been defined in adults and our patient's presentation was consistent with limited GPA (Table 1)[4].

Table 1. European Vasculitis Group/European League Against Rheumatism definitions for stages of granulomatosis with polyangiitis.

Limited	Restricted to the upper respiratory tract or lungs
Early systemic	Without organ- or life-threatening involvement
Generalized	Involves renal or other organ-threatening disease
Severe	Involves renal or vital organ failure
Refractory	Progressive and does not respond to standard treatment

Table 2. Differential diagnosis for persistent asymptomatic transaminitis[9].

Hepatic
Nonalcoholic fatty liver disease
Viral infections
Autoimmune hepatitis
Celiac disease
Inflammatory bowel disease
Wilson disease
Hemochromatosis
Cystic fibrosis
Alpha-1 antitrypsin deficiency
Metabolic diseases
Malignant infiltration of the liver
Toxins: drugs and alcohol
Iatrogenic: drug-induced liver injury
Extrahepatic
Myopathy
Adrenal insufficiency
Thyroid disease
Hemolytic disorders
Congestive hepatopathy

Of further interest is the persistent transaminitis after treatment initiation and normalization of inflammatory markers. GPA affecting the liver is rare, and in these patients, liver enzymes decrease toward normal after treatment initiation[6,7]. Hepatotoxicity is also a well-known complication of longterm MTX treatment[8]. However, this patient's liver enzymes were elevated prior to initiation of MTX. Differential diagnosis for persistent asymptomatic transaminitis in a child is listed in Table 2[9]. Further testing identified PI*ZZ phenotype in this patient, reflecting the most severe form of A1AT deficiency. Clinical presentation of liver disease in PI*ZZ A1AT deficiency is variable. Some children develop cholestatic jaundice and hepatitis as neonates. Some children, as in this case, present later in childhood with unexplained transaminitis. About 2–5% of PI*ZZ children progress to advanced fibrosis or cirrhosis requiring transplantation during childhood[9].

To our knowledge, this is the first published case of concurrent GPA and A1AT deficiency in a pediatric patient. Several case-control studies have established an association between GPA and A1AT deficiency phenotypes in adults[9]. Mean vasculitis activity was found to be greater in GPA patients with abnormal A1AT phenotype[10].

Given the documented association between GPA and A1AT deficiency, we propose screening pediatric GPA patients with persistent transaminitis for A1AT deficiency. At present, there is insufficient evidence to support enzyme augmentation or gene replacement therapies in the treatment of pediatric A1AT deficiency. However, early recognition may be useful for anticipating future disease activity, differentiating treatment-related hepatotoxicity from hepatitis due to A1AT deficiency, and implementing appropriate followup and monitoring.

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