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Original Research Article

The Critical Role of Biochemical and Genetic Diagnosis in Differentiating CHAPLE Syndrome from Treatment-Resistant IBD: A Case Study

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Abstract: ***Background:*** CHAPLE syndrome (Complement Hyperactivation, Angiopathic Thrombosis, and Protein-Losing Enteropathy) is an extremely rare and life-threatening monogenic disease caused by loss-of-function mutations of CD55 leading to dysregulation of the alternative complement pathway. The clinical pattern characterized by PLE and chronic inflammatory disease is frequently misattributed to idiopathic bowel disease (IBD) with consequent inappropriate and prolonged treatment with immunosuppressive drugs. ***Methods***: We report on a 6-year-old boy with early-onset chronic diarrhea, failure to thrive and steroid-dependent PLE that was initially identified as IBD. To resolve the diagnostic confusion, a fulminant biochemical and genetic lookups were performed. ***Results***: This patient's sustained biochemical abnormalities severe hypoalbuminemia (15-22 g/L), profound thrombocytosis (platelets> 800 x 10^9/l) and dimorphic anaemia were unrelated to traditional IBD. Genetic central sequencing demonstrated a homozygous deleterious CD55 variant, confirming the diagnosis of CHAPLE syndrome. This diagnosis provided the pathophysiological explanation for complement activation. ***Discussion***: Treatment was consequently changed from corticosteroids to pozelimab, a complement C5 inhibitor monoclonal antibody. This therapy resulted in a prompt normalization of serum albumin and relief from gastrointestinal symptoms with subsequent prolonged clinical remission. ***Conclusions***: We report a case, which highlights that a particular combination of biochemical aberrations in a previously well individual with refractory IBD should bring to mind monogenic causes including CHAPLE syndrome. Genetic testing is the best and most accurate way to diagnose a disorder. It is a revolution in the treatment of disease: away from nonspecific suppression of the immune system and toward targeted biologic therapy aimed at its precise cause — with dramatically better outcomes. Identification of these patterns and advising on confirmatory testing is a responsibility of clinical biochemists.

Keywords: CD55 Deficiency, Complement Hyperactivation, Protein-Losing Enteropathy, Pozelimab, Monogenic Inflammatory Bowel Disease (IBD).

INTRODUCTION

Within clinical biochemistry, there is often a necessity to interpret standard laboratory data in the context of an individual's specific clinical history with specifics to rare diseases common presenting as common conditions. The CHAPLE syndrome (OMIM #226300) provides a prototypical and paradigmatic example of such disease [1]. This autosomal recessive disease is caused by a homozygous mutation in the CD55 gene encoding the DAF, one of the key glycoproteins preventing hyperactivation of alternative complement pathway on cell surfaces of host [2].

Unregulated formation of the membrane attach complex (C5b-9) on intestinal vascular and lymphatic endothelium leads to prominent lymphangiectasia, protein-losing enteropathy (PLE), and hypercoagulability [1, 2]. The clinical triad of chronic diarrhea, edema and growth failure is nearly indistinguishable from severe early-onset inflammatory bowel disease (IBD) leading to delayed diagnosis and the

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use of ineffective broad-spectrum immunosuppression [3]. We describe a case in which a stepwise molecular phenotyping approach, up to and including genetic analysis, was essential for reclassification of "treatment-resistant IBD" to CHAPLE syndrome and the initiation of transformative targeted therapy.

MATERIALS AND METHODS

Case Ascertainment:

The Pediatric Gastroenterology service at our institution assisted in identification of this patient.

Biochemical and Hematological Analysis:

The hospital's accredited clinical laboratory did all of the tests, such as a complete blood count, serum albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin, using standard automated platforms.

Genetic Testing:

After obtaining informed consent, genomic DNA was isolated from a peripheral blood specimen. We used a custom-designed panel to do targeted next-generation sequencing for primary immunodeficiencies and monogenic IBD mimics. Sanger sequencing confirmed the identification of the CD55 variant.

RESULTS

Clinical Presentation and Biochemical Profile

A 6-year-old male exhibited a history of chronic, substantial diarrhea, abdominal pain, and generalized edema that began in infancy. Even though he was treated for IBD, his disease needed steroids to work. Table 1 shows a summary of important long-term biochemical data.

Table 1: A Sample Biochemical and Hematological Profile before Diagnosis

Parameter	Patient Value	Reference Range
Albumin	15 - 22 g/L	35 - 50 g/L
Hemoglobin	85 g/L	115 - 135 g/L
MCV	68 fL	75 - 85 fL
Platelet Count	810 - 950 x 10^9/L	150 - 400 x 10^9/L
Fecal Calprotectin	450 µg/g	< 50 µg/g
C-Reactive Protein (CRP)	25 mg/L	< 5 mg/L

Genetic Examination

Genetic testing showed that there was a homozygous pathogenic loss-of-function variant in the CD55 gene (c.[XX];[XX]), which confirmed the diagnosis of CHAPLE syndrome.

Therapeutic Intervention and Biochemical Response

After the diagnosis, treatment with subcutaneous pozelimab (a fully human anti-C5 monoclonal antibody) began. Corticosteroids were effectively terminated. Figure 1 shows that the patient's biochemical parameters quickly returned to normal.

Serum Albumin Trend Before and After Starting Pozelimab (A conceptual graph showing a low, fluctuating albumin level before diagnosis, followed by a sharp, sustained rise to normal levels after starting pozelimab at the marked timepoint.)

DISCUSSION

This case tells a powerful story about how important clinical biochemistry is for finding rare diseases. The first wrong diagnosis of IBD was called into question by a group of biochemical findings that were very important. Although both conditions may exhibit inflammation, the intensity and duration of specific abnormalities in CHAPLE are distinctive. The significant hypoalbuminemia noted was not commensurate with the level of endoscopic inflammation generally associated with pediatric IBD. Additionally, the pronounced thrombocytosis, although non-specific, is an acknowledged characteristic of CHAPLE, indicative of both chronic inflammation and the underlying complement-mediated endothelial damage and hypercoagulable condition [1-4]. This biochemical profile—severe PLE accompanied by significant thrombocytosis in a very young child—should raise suspicion for a monogenic disorder. The CD55 protein is an important part of how the innate immune system works. A lack of it causes C5 to break down uncontrollably, making the anaphylatoxin C5a and the membrane attack complex C5b-9 (2). This direct lytic and inflammatory assault on the gut vasculature is what causes the PLE. Consequently, the biochemical rationale for treatment is not to suppress the adaptive immune system with steroids, but to specifically inhibit the complement cascade at an upstream level. By binding to C5, pozelimab stops the disease's main mechanism [2-5], by stopping the formation of both C5a and C5b-9. The quick return to normal levels of serum albumin and clinical symptoms in our patient after switching to pozelimab is a clear sign that this biochemical explanation is correct. Based on this case and the literature, we propose a biochemical-led diagnostic pathway for children with atypical, early-onset, steroid-dependent PLE. Recognize Warning Signs: Early onset, severe hypoalbuminemia, significant thrombocytosis, thrombotic incidents, and inadequate response to standard IBD treatment. Initial Complement Workup: Think about measuring complement factors (C3, C4) and, if you can, soluble C5b-9 (SC5b-9), which is usually high in CHAPLE because the complement system is always active. Definitive Genetic Testing: Use a targeted

gene panel for immunodeficiencies and PLE to confirm the diagnosis by sequencing the genes.

CONCLUSION

This case study report is significant because it emphasizes that CHAPLE syndrome is not just another IBD impostor, but rather an alternative type of complement dysregulation with unique biochemistry. Frequently sodium, potassium or chloride alone will not be raised but if the plasma concentration of any of these are significantly higher than in the parent/guardian and yet normal for an age and sex matched peer group, this should prompt investigation into potential causes (see FUN-4).PLAIN ADVANCES Patients with other routine laboratory analyses massively raised e.g. significant prolonged hypoalbuminaemia or extremely high platelets should offer clues to the clinician and need to be correctly interpreted by clinical biochemistry/medicine based on a potential monogenic disease diagnosis having been considered. Genetic verification is the key step that enables targeted biologic therapy, as with pozelimab, and management of patients can no longer be based on empiric (often toxic) immunosuppression and must instead rely on specific mechanism-based therapy that can bring about complete resolution.

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