New onset IBD in 19 years old female with colon perforation, multi-organ thrombi and possible catastrophic antiphospholipid syndrome, concerning for genetically driven immune dysregulation.

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BACKGROUND

- IBD may be a manifestation of a genetically driven immune disorder (GID).
- We present a case of previously healthy 20-years old female with new onset IBD acutely complicated by colon perforation and hemorrhagic shock, renal failure and acute liver injury secondary to multi-organ thrombi likely due to catastrophic antiphospholipid syndrome.

CASE PRESENTATION

- **Baseline**: Previously healthy 20-year-old South Asian female, PMH: allergic rhinitis
- **Initial Symptoms**:
  - 6-month history of constipation, abdominal pain, and rectal bleeding.
  - Worsening symptoms with low-grade fevers prompted hospital admission.
- **Initial Workup**:
  - CT: Pancolitis; Colonoscopy: Diffuse inflammation in descending and rectosigmoid colon with unusual purple mucosal discoloration → concern for GI vasculitis.
  - Findings consistent with IBD, though subtype remained unclear.
  - Lab: Positive cardiolipin IgM, elevated D-dimer, PT , INR; no schistocytes.
- **Early Treatment**:
  - IV steroids and infliximab → initial improvement.
- **Acute Decompensation**:
  - Colon perforation (pneumoperitoneum) with hemorrhagic shock from GI bleeding.
  - Hepatic and renal thrombi → acute liver and kidney failure, required CRRT.
  - Infectious workup: Norovirus, EPEC, bacteremia, candida (in spleen colture).
- **Interventions**:
  - Subtotal colectomy with end ileostomy.
  - Treated for possible catastrophic antiphospholipid syndrome (CAPS) with plasmapheresis, high-dose steroids, and heparin.
  - Multiple emergent laparotomies for intra-abdominal hematomas.
- **Pathology**:
  - Transmural colitis → suggestive of Crohn's disease.
  - Incidental 1.5 mm neuroendocrine tumor (NET) of the appendix
- **Hospitalization Outcome**:
  - Full clinical recovery.; No recurrence of symptoms.
  - Off immunosuppressive / disease modifying treatment and anticoagulation therapy.

GENETIC TESTING

Gene, Transcript	Mode of Inheritance (OMIM)	DNA Variant (Zygosity)	ClinVar ID	Highest Allele Frequency (gnomAD)	In Silico Prediction	Interpretation
LRBA, NM_006726.4	AR, 606453	c.8257C>T, p.His2753Tyr (Heterozygous)	3291217	0.075% (East Asian)	Conflicting	Uncertain
LRBA, NM_006726.4	AR, 606453	c.1154G>T, p.Gly385Val (Heterozygous)	Not listed	0.0100% (South Asian)	Conflicting	Uncertain
TNFAIP3, NM_006290.3	AD, 191163	c.1753G>A, p.Asp585Asn (Heterozygous)	2171326	0.0062% (African)	Tolerated	Uncertain

Table 1: Genetic results - IEI/PID panel, confirmed by WGS.

B CELL PHENOTYPING

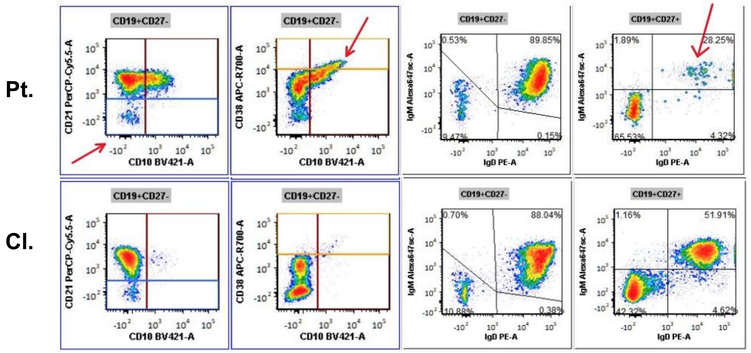

Figure 1: B Cell Phenotyping - patient exhibit small expansion of "autoreactive" (CD21-) B cells [~6% vs 2%, left panel]; higher early transitional B cells i.e. T1/T2 transitional cells (CD38+CD10+)[~8% vs 1%, left to middle panel]; much reduced non-switched memory b cells (CD27+IgM+IgD+) [right panel). Also mildly elevated CD21dim B cells (data not shown).

Special thanks to Dr. Samuel Chiang (Cincinati Children's) for sample analysis (figure 1) and CTLA-4 levels data (figure 2)

FUNCTIONAL STUDIES: CTLA-4 LEVELS

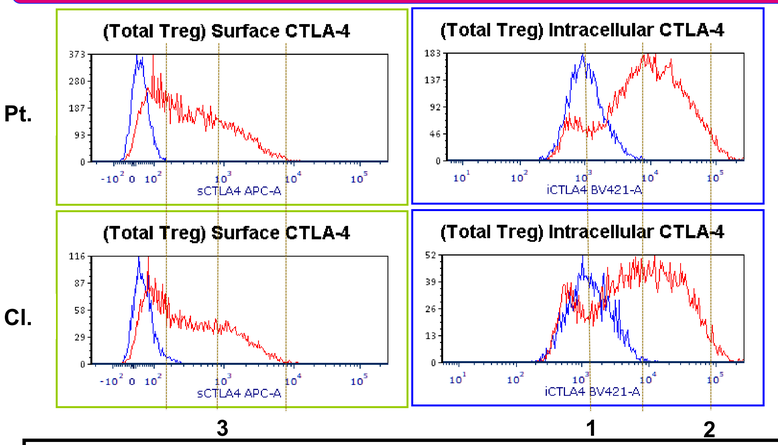

Figure 2: CTLA-4 Levels – similar level of intracellular CTLA-4 levels seen in resting and activated Treg (right 1,2) as well as activated surface Treg (left, 3)

DISCUSSION

We present a case of IBD with atypical extraintestinal manifestations (multiorgan thrombi, complement activation, and an incidental NET. Immunophenotyping revealed increased early transitional T1/T2 B cells and expansion of $CD21^{-}$ and CD21dim B cells, suggestive of an autoreactive process. Inflammatory cytokines (IL-10, IL-8, IL-6, IL-13) were modestly elevated. Genetic testing identified two LRBA missense variants of uncertain significance and phasing with normal CTLA-4 expression. A third VUS was found in TNFAIP3, which encodes A20, a negative regulator of NF-κB signaling. While truncating TNFAIP3 mutations cause a Behçet-like autoinflammatory syndrome, the pathogenicity of this variant remains unclear and will be the focus of future work in the effort to obtain molecular diagnosis for this patient.

REFERENCES

PMID: 27845235, 26642243, 29241730, 26768763