NBAS-associated Disease Manifesting with Evans Syndrome

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BACKGROUND

Neuroblastoma amplified sequence (*NBAS*)-associated disease is a multisystem disorder that may involve the liver, nervous system, immune system, retina, connective tissue and bone. The most commonly reported immunologic aberrations are hypogammaglobinemia and NK cell deficiency. Hematologic features of isolated ITP or AIHA are rare, although the Pelger-Huet anomaly is frequently visualized on peripheral smear.

Here, we present a case of 25-year-old male with CVID and Evans syndrome (ES) with ITP and warm AIHA who was referred for further evaluation due to serious recurrent infections despite adequate IgG supplementation and refractory ES.

CASE PRESENTATION

The patient was diagnosed with CVID requiring immunoglobulin replacement at age 8 years and Evans syndrome (ES) with ITP and warm AIHA at age 16 years. His ES required treatment with corticosteroids, vincristine, danazol, rituximab and splenectomy, with an ongoing need for chronic steroids to manage hemolysis.

CASE PRESENTATION (cont)

Additionally, he has legal blindness secondary progressive optic nerve atrophy, short stature, liver disease, type 1 diabetes mellitus and lymphopenia. He had serious recurrent infections despite adequate IgG supplementation (IgG > 1000 mg/dL) and refractory ES. Laboratory evaluation (table 1) was notable for severe lymphopenia, undetectable IgA & IgM, DAT w/ 2+ IgG & negative C3 and multiple positive autoantibodies. Peripheral smear demonstrated easily appreciable neutrophils with the Pelger-Huet anomaly (figure 1).

Genetic testing for immune disorders identified a pathogenic heterozygous variant in *NBAS* c.2827G>T, p.Glu943Ter, along with a heterozygous missense variant of uncertain significance in *NBAS* c.5740C>T, p.Arg1914Cys, consistent with the *NBAS*-associated disease.

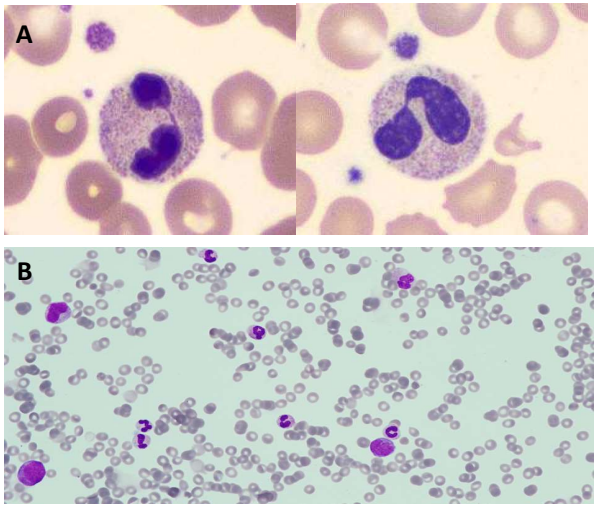

Figure 1. Pelger-Huet anomaly (bi-lobed nuclei with "pince-nez" appearance) seen in the peripheral smear (A) and bone marrow aspirate (B) of our patient.

Table 1

Flow cytometry	
	CD3+ T cells 128 cells/mcL (ref: 550-2202 cells/mcL)
	CD4+ T cells 62 cells/mcL (ref: 365-1437 cells/mcL)
	CD8+ T cells 65 cells/mcL (ref: 199-846 cells/mcL)
	CD19+ B cells 0 cells/mcL (ref: 91-109 cells/mcL)
	CD16/56+ NK cells 39 cells/mcL (ref: 59-513 cells/mcL)
Immunoglobulins	
	IgA < 2 mg/dL (ref: 40-350 mg/dL)
	IgM < 10 mg/dL (ref: 50-370 mg/dL)
	IgG 1222 mg/dL (ref: 620-1520 mg/dL)
	IgG1 621 mg/dL (ref: 340-1000 mg/dL)
	IgG2 341 mg/dL (ref: 100-540 mg/dL)
	IgG3 30.5 mg/dL (ref: 20-170 mg/dL)
	IgG4 14.3 mg/dL (ref: 6-130 mg/dL)
DAT	
	IgG POS2+
	C3 negative
	Polyspecific POS2+
Autoantibody testing	
	Anti-E (RH3) +
	Anti-K (KEL1) +
	Platelet autoantibody + (IIb/IIIa, Ib/IX, Ia/2a detected in eluate)
	Anti-GAD65 +
	ANA negative
ALPS DNT screen negative	

Ref = reference range, ALPS = autoimmune lymphoproliferative syndrome, DNT = double negative T cell, ANA = antinuclear antibody

CONCLUSION

Immune-mediated cytopenias, particularly in association with hypogammaglobinemia, liver disease, optic atrophy and/or the presence of the Pelger-Huet anomaly, should prompt consideration for *NBAS*-associated disease as the underlying etiology

The missense variant identified in our patient occurs in the c-terminal region, at the same codon as the Yakut founder variant, *NBAS* c.5741G>A, p.1914His. C-terminal missense variants, in conjunction with null variants, define a phenotype-genotype group characterized by highly penetrant, pleiotropic, multisystem features.

This case demonstrates the value of genetic testing in adult patients with unexplained hypogammaglobinemia as well as review of the peripheral blood smear as a diagnostic aid.

REFERENCES

1. Staufner C, Peters B, Wagner M, et al. Defining clinical subgroups and genotype-phenotype correlations in NBAS-associated disease across 110 patients. *Genet Med*. 2020;22(3):610-621. doi:10.1038/s41436-019-0698-4