A unique pathogenic heterozygous hyou1 mutation presenting with recurrent osteomyelitis.

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Introduction

Several genetic mutations have been linked to recurrent infections that vary in severity from mild to life threatening. The HYOU1 is a gene that encodes a chaperone protein that is involved in mediating cell stress within the endoplasmic reticulum and mitochondria. The mechanism of this protein is accomplished by reducing oxidative stress on cells and aiding in unfolded protein responses.[1]

A previous case report identified a homozygous hyou1 mutant that presented with anemia, thrombocytopenia and leukopenia resulting in severe immunodeficiency, repeated infections and ultimately death.[2] Another case of an hyou1 mutant reports a 45-year-old female with recurrent infections and bouts of hypoglycemia throughout her life.[1]

Our patient presented to the office for shortness of breath and after history taking and laboratory evaluation, we were able to ascertain a history of chronic infections, hypoglycemia and a genetic mutation in hyou1.

Case Report

We present a case of a 32-year-old female with chronic shortness of breath, a history of recurrent osteomyelitis, chronic sinusitis, and medically managed hypoglycemia. The patient experienced frequent sinus infections that responded to 10-day courses of Augmentin. Allergy testing was negative for common allergens, but she has a history of hives in response to clindamycin, Keflex, and sulfa drugs. Her medical history also includes polycystic ovarian syndrome and attention-deficit disorder. She was using Triple inhaler (ICS/LABA/LAMA) for possible asthma, which she reported improved her symptoms.

The patient's history includes 20 surgeries with frequent intubations due to osteomyelitis. Her family history is notable for hypoglycemia, arthritis, and Hashimoto's thyroiditis. To investigate her shortness of breath, a pulmonary function test was performed. She reported improvement with albuterol during the office visit. She also underwent an immunodeficiency panel to evaluate potential causes of her recurrent infections and a genetic evaluation.

Additionally, she was referred to ENT who diagnosed her with subglottic stenosis, due to chronic infection, which was deemed untreatable surgically. Cultures were taken from the infection site, and appropriate antibiotics were initiated.

Results

Investigative results indicated a fixed airway obstruction (Fig. 3) and a heterozygous pathogenic mutation in the HYOU1 gene (exon23,c.2638G>A) (p.Ala880Thr) (Fig.1), normal immunoglobulin levels, lymphocyte subpopulations and neutrophil oxidative burst assay within normal ranges. A CBC and BMP came back normal. Cultures from a laryngeal biopsy were positive for several microorganisms including Klebsiella and methicillin resistant staphylococcus aureus (MRSA) (Fig 2).

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
HYOU1	c.2638G>A (p.Ala880Thr)	heterozygous	Uncertain Significance

Fig. 1: Results from genetic analysis displaying hyou1 genetic mutation.

Specimen: **Swab - Larynx biopsy specimen (specimen)**

Component	6 mo ago
Culture, Wound	**Many Klebsiella (enterobacter) aerogenes !**
Culture, Wound	**Few Methicillin resistant Staphylococcus aureus !**
Culture, Wound	**Few normal respiratory flora**
Gram Stain	**Many Gram positive cocci !**
Gram Stain	**Many Gram negative bacilli !**
Gram Stain	**Few Gram positive bacilli !**
Gram Stain	**Rare Polymorphonuclear leukocytes !**

Fig 2: Culture report from laryngeal biopsy

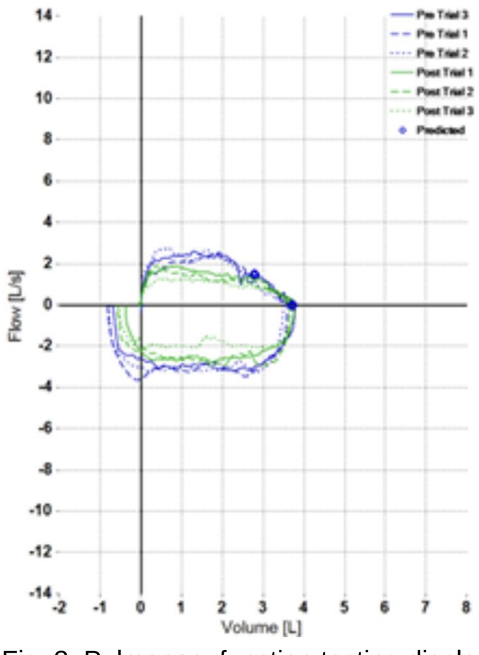

Fig. 3: Pulmonary function testing displaying fixed airway obstruction

Discussion

Patients with homozygous mutations in HYOU1 have previously presented with hypoglycemia and severe, life-threatening immunodeficiencies. The HYOU1 gene encodes a chaperone protein involved in cell homeostasis, located in the endoplasmic reticulum and mitochondria.

Our patient presented with shortness of breath, and it was later elicited from history that she had chronic infections and hypoglycemia. This constellation of symptoms prompted pulmonary function testing and an immunology panel to investigate the cause of her recurrent infections. Although the immunology panel returned normal results, genetic testing revealed a heterozygous mutation in HYOU1. This genetic finding led to a review of previous cases with homozygous HYOU1 mutations, which showed a similar collection of symptoms. Her pulmonary function test indicated subglottic stenosis, and she was referred to ENT. On bronchoscopy, ENT findings revealed a subglottic stenosis.

Given her history of the genetic mutation, we propose that her recurrent osteomyelitis, infectious subglottic stenosis, and medically treated hypoglycemia are linked to her pathogenic heterozygous HYOU1 mutation. The patient was started on prophylactic ciprofloxacin, with noted improvements.

Conclusion

This is the first reported case of a unique pathogenic heterozygous HYOU1 mutation presenting with recurrent osteomyelitis, chronic subglottic infections and medically treated hypoglycemia. This patient is subjectively improving on prophylactic ciprofloxacin.

References

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