An Interesting Presentation of Chronic Granulomatous Disease

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Case

A 2 year old boy presents to the hospital with fever of unknown origin. At the age of one, he had cervical lymphadenitis that grew mssa that was responsive to antibiotics.

For a three month period, he had ongoing persistent daily fevers to 103. He was admitted and extensively worked up for multiple infections with no identifiable source. He was then readmitted with ongoing fever, lethargy and abdominal distension. He underwent an exploratory laparatomy with biopsy results of the peritoneum showing peritonitis and granulomas.

A NOBA revealed an abnormal response to stimulation. He was diagnosed with Chronic Granulomatous Disease

He recently had a younger brother who was just born and was reportedly healthy.
Mom and Dad were not related.

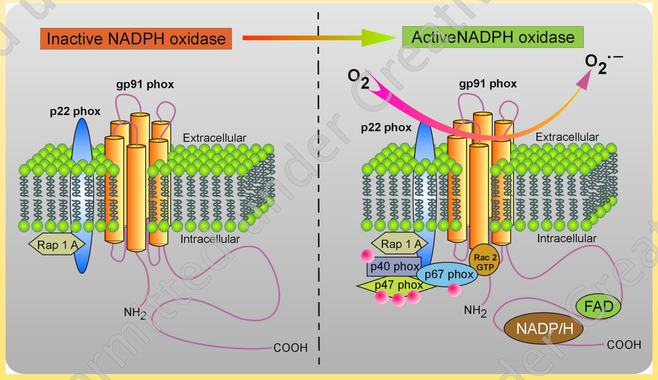
Background

Chronic granulomatous disease is an inherited disorder of the NADPH oxidase characterized by severe bacterial and fungal infections and excessive inflammation. CGD affects approximately 1/200,000 persons. It was first described in the 1950's as a fatal granuloimatous disease of childhood. Neutrophils from CGD patients fail to show an increase in oxygen consumption and hydrogen peroxide formation. This rapid oxygen consumption has been linked to the NADPH oxidase. The phagocyte NADPH oxidase functions to rapidly generate superoxide anions by transferring electrons from NADPH to molecular oxygen. The cytochrome of NADPH oxidase, composed of gp91phox and p 22 phox, is embedded in the cell membrane.

Background

Upon activation of the oxidase, the cytoplasmic subunits p47 phox, p67 phox, and p40 phox appear to translocate to the membrane-bound cytochrome. Activation of rac, a member of the lower molecular weight GTP-binding proteins and translocation of rac to the membrane-bound cytochrome are also critical for NADPH oxidase activation. CGD results from disabling mutations in genes encoding phox proteins. Approximately two thirds of CGD cases are X-linked (gp91phox deficient) and the remainder are autosomal recessive.

Defects result in decreased production of superoxide, hydrogen peroxide, hydroxyl radical and hypochlorite ion within neutrophils and macrophages. Genetic mutations within the CYBB or CYBA genes result in malfunction of one of the phagocyte NADPH oxidase components.



Diagnosis

Early diagnosis is extremely important.
CGD should be suspected in patients with recurrent or unusually severe infections, such as a liver abscess caused by staphlyococcus aureus.
Specific opportunistic infections should prompt evaluation for CGD including invasive mold diseases, infections by B. Cepacia, S. Marescens, and Nocardia species in the absence of a known immunodeficiency.
Inflammatory disorders such as inflammatory bowel disease at an early age and granulomatous cystitis can be manifestations of CGD.
Family history of males with severe or unusual infections can be a clue to the diagnosis of X linked CGD
Consanguineous parents increases the risk for autosomal recessive disorders

Diagnostic tests:
NOBA (neutrophil oxdiative burst assay) via flow cytometry: the disease is indicated by absence or significant alteration of activity. The blood sample must remain ambient and be tested within 48 hours of collection
Genetic testing: CYBB or CYBA genes result in a malfunction of one of the phagocyte NADPH oxidase components

Clinical Manifestations

CGD patients are susceptible to a spectrum of bacterial and fungal infections.
Paitents with the X-linked form of CGD appear to be at greater risk for infections and early mortality compared to patients with autosomal recessive forms of CGD.
According to a US registry of 368 patients with CGD, pneumonia was the most frequent type of infection, occurring in 79% of patients, with Aspergillus species being the most common cause. Fifty three percent of patients had suppurative adenitis, 42% had a subcutaneous abscess, and 27% had a liver abscess. Staphylococcus aureus was the most common cause of soft tissue and liver abscesses.

Clinical Presentation

CGD is also characterized by exuberant inflammatory responses leading to granuloma formation, such as granulamatous enteritis resembling Crohn's disease and genitourinary obstruction.

Mulch pneumonitis is a recently described life-threatening hyperinflammatory response to fungal pneumonia in CGD, requiring antifungal and systemic steroids.

Treatment

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Early diagnosis and aggressive therapy, including use of fungal and bacterial prophylaxis, markedly improves prognosis

Trimethoprim-sulfamethoxazole is the recommended agent for antibacterial prophylaxis. If trimethoprim-sulfamethoxazole can't be used, dicloxacillin is a recommended alternative.

Itraconazole is recommended for antifungal prophylaxis.

HCT provides curative therapy for patients with CGD

Case Follow-up

The patient underwent genetic testing and was found to be hemizygous for a duplication of a single G nucleotide in exon 13 of the CYBB gene. Based on this information, he was thought to have the X linked form of CGD. His younger brother was tested with a NOBA that returned positive and he was started on bacterial and funal prophylaxis.