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Streptococcal Infections in Patients with Chronic Granulomatous Disease: Case Report and Review of the Literature

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Abstract

Streptococcus intermedius caused a liver abscess in a patient with chronic granulomatous disease (CGD). In contrast to typical staphylococcal abscesses in CGD, this abscess was liquid, easily drained, and resolved without surgery or steroids. This case and literature review provide insight into this organism's pathogenesis, including in CGD.

Keywords

Chronic granulomatous disease; liver abscess; streptococcus intermedius

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Conflicts of Interest The authors declare that they have no conflict of interest.

Introduction

Chronic granulomatous disease (CGD) is a phagocyte defect characterized by recurrent life-threatening bacterial and fungal infections due to defective NADPH oxidase activity, and impaired superoxide and downstream hydrogen peroxide (H₂O₂) production [1]. This defect can be inherited as an X-linked trait, affecting the NADPH oxidase gp91^{phox} subunit (*CYBB* [cytochrome b-245, alpha polypeptide]), or as an autosomal recessive trait, affecting the remaining NADPH oxidase subunits (p22^{phox} (*CYBA* [cytochrome b-245, beta polypeptide]), p47^{phox} (*NCF1* [neutrophil cytosolic factor 1]), p67^{phox} (*NCF2* [neutrophil cytosolic factor 2]), and p40^{phox} (*NCF4* [neutrophil cytosolic factor 4]) [2]. The recurrent infections in patients with CGD primarily affect the lung, skin, lymph nodes and liver, and are typically due to a rather narrow spectrum of bacteria and fungi, including *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia* complex, *Nocardia* species and *Aspergillus* species [3].

In contrast to patients with CGD, pyogenic liver abscesses in the general population are typically polymicrobial. Commonly isolated pathogens include members of the *Streptococcus anginosus* group (formerly known as the *Streptococcus milleri* group), *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae* and *Candida* species [4].

We report a case of a liver abscess in a patient with CGD caused by *Streptococcus intermedius*, a member of the *Streptococcus anginosus* group. We also provide a review of reported cases of streptococcal infections in patients with CGD. *Streptococcus intermedius* is a usual suspect causing liver abscess in an unusual host, a finding that reinforces the importance of microbiologic identification of all liver abscesses in CGD.

Case Report

A 27 year-old Caucasian man presented with one week of fevers, rigors, diaphoresis, malaise and generalized fatigue while on prophylactic trimethoprim-sulfamethoxazole and levofloxacin. He was diagnosed with X-linked CGD (*CYBB* c.1234 G>C; p.G412R in the middle of exon 10) at three months because of perirectal abscesses. At one year he developed a *Staphylococcus aureus* liver abscess, and six months later a *Burkholderia cepacia* complex pneumonia. At age 20 a right upper lobe cavitory lesion was detected, which was eventually resected at 26 years. CGD colitis had been present for several years and was treated with mesalamine. He had no history of sick contacts, foreign travel, recent dental or surgical procedures and had been clinically well for one year prior to his current presentation.

He was febrile and diaphoretic (39.5 C), but otherwise well. Laboratory data on admission showed elevated liver enzymes (alanine aminotransferase 166 IU/L, aspartate aminotransferase 195 IU/L) and inflammatory markers (erythrocyte sedimentation rate 95 mm/h and c-reactive protein 272 mg/L). Computed axial tomography (CT) of the abdomen with intravenous contrast showed an abscess in the posterior right hepatic lobe with enlarged portocaval lymph nodes. Gadolinium-enhanced magnetic resonance imaging (MRI) of the

abdomen confirmed a 6.5×5×4.5 cm abscess with subcentimeter satellite lesions communicating with the dominant abscess cavity (Fig. 1a). The abscess was biopsied and a drain placed percutaneously under CT guidance, releasing 90 ml of green mucopurulent fluid. Gram stain showed neutrophils with many gram-positive cocci in pairs and chains. Pinpoint alpha hemolytic colonies were seen after 48 h on sheep blood agar, with a distinctive butterscotch smell. One set of blood cultures grew gram-positive cocci in pairs and chains at 23 h. The API 20 Strep system (bioMerieux, Inc Hazelwood, MO) did not yield an acceptable identification score in conjunction with biochemical testing (catalase: negative, esculin: positive). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using a MALDI-TOF MicroFlex LT mass spectrometer (Bruker Daltonics, Billerica, MA) identified *Streptococcus anginosus* group with high score (~2.0). Partial sequencing of the 16S rRNA gene (~500 bp) showed 100% match to *Streptococcus intermedius* type strain.

H₂O₂ production in the *Streptococcus intermedius* isolate was assessed using the method described by McGroarty et al. [5]. *Streptococcus intermedius* isolates from both the liver abscess and blood cultures were compared to *Lactobacillus jensenii* (positive control) [5] and *Hemophilus paraprophilus* (negative control) isolates [6]. With this method, H₂O₂-producing colonies and their surroundings turn blue. In our case, only the *Lactobacillus jensenii* colonies developed a blue pigment, a finding that supports the previously reported lack of H₂O₂ production in *Streptococcus intermedius* isolates [7].

E-test® (Biomérieux Diagnostics, Marcy l’Etoile, France) showed that the isolate was susceptible to penicillin (minimal inhibitory concentrations in µg/ml [MIC]00.008), ceftriaxone (MIC00.125), meropenem (MIC00.016) and vancomycin (MIC01.0) but resistant to both clindamycin (MIC>256) and levofloxacin (MIC>32).

Following the sampling and initial drainage of the abscess, antibiotic coverage was initiated with vancomycin, clindamycin and meropenem. Five days later, antibiotics were narrowed to meropenem, and finally to penicillin G once speciation and sensitivities were confirmed.

The patient remained febrile for the first 7 days of his hospitalization with a maximum temperature of 41.3 C. Surveillance blood cultures were negative and follow up CT scan of the abdomen obtained two weeks after removal of the drain showed a significant decrease in size of the abscess, with inflammation tracking along the site of the hepatic drain (Fig. 1b). Given the patient’s history of CGD colitis, a colonoscopy was performed to evaluate for a potential source for the patient’s bacteremia and liver abscess. He had mild focal active colitis and several small poorly formed granulomata along with typical collections of pigmented macrophages in the rectum and ascending colon. The patient was discharged on an eight-week course of amoxicillin and probenecid. Liver MRI obtained one month after his discharge showed only a residual 3.5× 1.5×1.5 cm mildly enhancing lesion without central fluid collection (Fig. 1c), and subsequent studies have shown complete resolution.

Literature Review

A literature review of streptococcal infections in patients with CGD was performed using the Medline/PubMed database. Searches were performed using the terms “chronic granulomatous disease” and “streptococcus”. Our search yielded 5 reports of streptococcal infection in patients with CGD (Table I). We identified only two other cases of *Streptococcus anginosus* group pyogenic liver abscesses in patients with CGD. In one case, the organism was identified as *Streptococcus intermedius* [8], while in the other, the organism was simply identified as belonging to the *Streptococcus anginosus* group [9]. In addition, one case of *Streptococcus intermedius*-brain abscess in a patient with CGD has also been reported [10]. All patients with *Streptococcus anginosus* group infections were treated with antibiotics and survived. Amongst the reported cases of streptococcal infections in patients with CGD, one patient died at 40 days of life of invasive group B streptococcus disease. The patient had surgery on an abscess of the anal margin, which grew out *E. coli* and *Klebsiella pneumoniae*, 20 days earlier [11].

Discussion

CGD patients are generally prone to infections by catalase-producing organisms, which are thought to degrade both microbial and host H₂O₂. Host-derived H₂O₂ in the phagolysosome is created by metabolism of the superoxide generated by the NADPH oxidase. Streptococcal infections are thought to be rare in CGD because these catalase-negative, H₂O₂-producing bacteria produce H₂O₂ which complements the superoxide production defect in CGD cells. However, *Streptococcus intermedius* is a H₂O₂ non-producing organism [7, 10], which may explain its pathogenicity in CGD. A similar situation has been described for *Hemophilus paraphrophilus* infection in patients with CGD [6].

Although streptococci are inherently catalase negative, the ability to produce H₂O₂ depends on the strain. Whiley et al., found that only 34 of 47 strains of *Streptococcus anginosus* produced H₂O₂, compared to 6 of 49 strains of *Streptococcus constellatus*, but none of the 61 strains of *Streptococcus intermedius* [7]. Interestingly, of the three subspecies listed, *Streptococcus intermedius* was especially associated with abscess formation, hematogenous spread and deep seated infections in the general population [12]. The reason for this predisposition to abscess formation is unclear, but may be related to toxic interactions with polymorphonuclear leukocytes [13]. Moreover, *Streptococcus intermedius* isolates from our patient did not produce H₂O₂. These findings confirm important biologic variation within the *Streptococcus anginosus* group, supporting the value of definitive speciation, such as by 16S rRNA sequencing.

Streptococcus anginosus infections often follow dental or gastrointestinal procedures. We hypothesize that our patient's CGD colitis may have been a risk factor for bacterial seeding from the gastrointestinal tract to the liver. However, given the considerable prevalence of colitis in patients with CGD, this would not explain why *Streptococcus anginosus* is seen so infrequently in CGD.

The course and response to treatment in this case was very different than that of CGD patients with the more typical staphylococcal liver abscesses [14]. *Staphylococcus aureus* is the most common pathogen in CGD liver abscesses, which are typically difficult to treat. They usually require surgical resection, in addition to antibiotics, or systemic corticosteroids for complete resolution [15]. Our patient's response to antibiotics and drainage alone was more rapid and less complicated than commonly seen with staphylococcal liver abscess in CGD. Moreover, our patient developed a *Streptococcus intermedius* liver abscess while on prophylactic levofloxacin. Although there is little data on the susceptibility of *Streptococcus intermedius* to quinolones, a study involving 180 clinical isolates of *Streptococcus anginosus* (29 of them *Streptococcus intermedius*) revealed 17.3% resistance of *Streptococcus intermedius* to ciprofloxacin [16]. Thus, it is possible that prophylactic levofloxacin may have predisposed our patient to a resistant strain of this organism.

This *Streptococcus intermedius* liver abscess in a patient with CGD is an example of a common pathogen causing disease in an uncommon host. Speciation within the *Streptococcus anginosus* group can lead to a better understanding of its pathogenesis in CGD and suggests that microorganisms other than *Staphylococcus aureus* should be considered in liver abscesses in patients with CGD.

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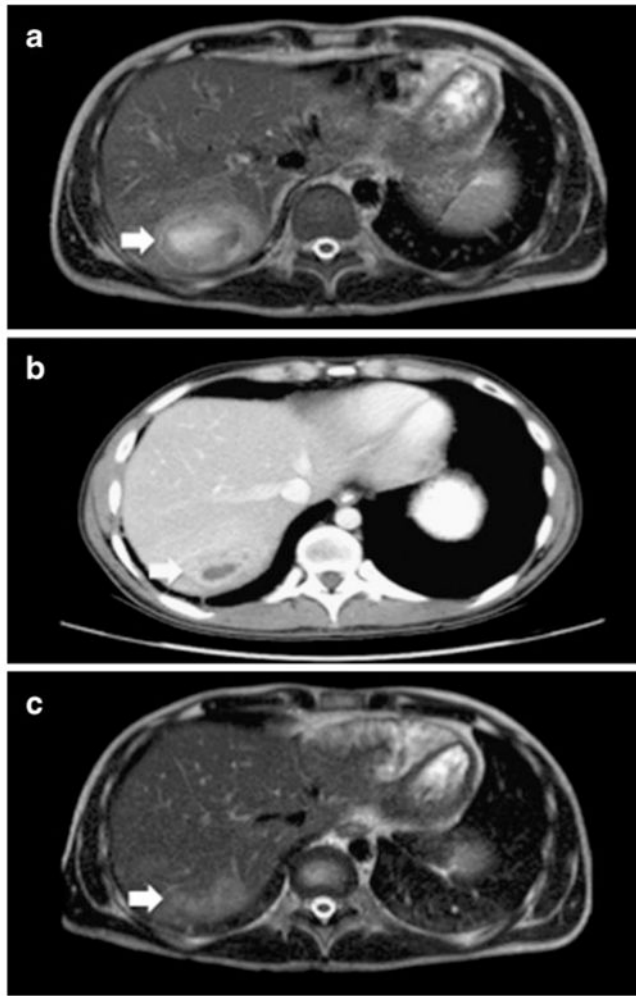


Fig. 1. a MRI of the abdomen on admission. T2 heterogeneously hyperintense lesion measuring 6.5×5×4.5 cm within hepatic segment VIII, compatible with liver abscess. b CT scan of the abdomen two weeks after removal of percutaneous drain. c MRI of the abdomen one month after discharge. Residual 3.5×1.5×1.5 cm area of moderately increased T2 hyperintensity visible at the previous site of the abscess with mild enhancement but no central fluid collection

Streptococcal infections in patients with CGD

Table 1

Reference	Age/Gender	Genetics	Presentation	Pathogen	Treatment	Outcome
Present case	27 y/male	X-linked	Liver abscess	<i>Streptococcus intermedius</i>	Penicillin G followed by amoxicillin and probenecid	Survived
[8]	12 y/male	Not specified	Liver abscess	<i>Streptococcus intermedius</i>	Surgery and antibiotics	Survived
[10]	20 y/male	X-linked	Brain abscess	<i>Streptococcus intermedius</i>	Carbapenem and granulocyte transfusion	Survived
[9]	4 mo/female	Not specified	Liver abscess	<i>Streptococcus anginosus</i> group	Ceftazidime and clindamycin	Survived
[17]	14 y/male	Autosomal recessive (not specified)	Mastoiditis and left postauricular abscess	<i>Streptococcus viridans</i>	Ceftriaxone	Survived
[18]	46 y/female	Autosomal recessive (p47 ^{phox})	Cervical adenitis Liver abscess	<i>Streptococcus viridans</i> <i>Streptococcus mitis</i>	Unspecified Percutaneous drainage and antibiotics	Survived
[11]	35 d/male	Not specified	Bacteremia meningitis	<i>Group B Streptococcus</i>	Ampicillin, gentamicin cefotaxime	Died