

# Chronic granulomatous disease with recurrent hepatic abscesses in an adult

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## ABSTRACT

Chronic granulomatous disease (CGD) is a condition of inability to deal with bacterial and fungal infections, due to defective respiratory burst in neutrophils leading to recurrent cutaneous and visceral infections. Usually a disease of childhood, but patients nowadays survive to adulthood, and diagnosis might be difficult if not considered. We describe a 20-year-old female with previously undiagnosed CGD, presenting with recurrent cutaneous and hepatic abscesses.

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Chronic granulomatous disease (CGD) is a rare inherited disorder in which phagocytes fail to produce hydrogen peroxide, and is characterized by widespread granulomatous lesions of the skin and other organs, hypergammaglobulinemia, anemia, leukocytosis, and defective killing of catalase-producing bacteria (such as *Staphylococcus aureus* [*S.aureus*], *Serratia*, *Escherichia coli*, and *Pseudomonas*), and fungi.<sup>1</sup> This may lead to life threatening infections including hepatic abscesses.<sup>2</sup> This hereditary disorder can be transmitted with an inheritance pattern of either an autosomal or an X-linked disease, depending on the molecular defect.<sup>3</sup> We present a case of a young female with CGD, and recurrent hepatic as well as extensive cutaneous abscesses. The objective of this report is to

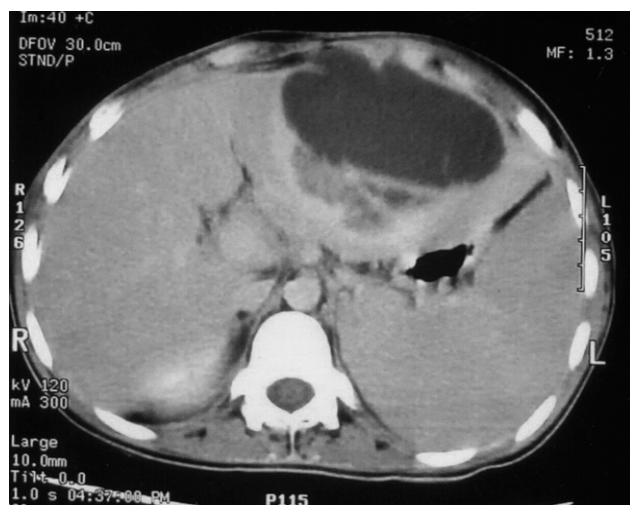
emphasize that these patients nowadays can survive to adulthood, if diagnosed and treated early.

**Case Report.** A 20-year-old, single, female Yemeni, presented to the accident and emergency department of Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia (KSA), with a 2 months history of fever and left upper abdominal pain. The fever had been constant, and associated with drenching night sweats. She had received oral antibiotics, which she took at irregular intervals, with no improvement. The pain was described as dull and aching, waxing and waning, without relieving factors. Her past medical history was remarkable for a similar illness diagnosed as a liver abscess when she was 7 years of age. She also had recurrent skin abscesses for as long as she could remember. Further cardiac catheterization was performed in Riyadh Military Hospital, Riyadh, KSA, for treatment of a valvular ailment in childhood. She was a product of a full term, normal, spontaneous, vaginal delivery, with consanguineous parents. She had been fully immunized. Her 4 other siblings were alive and well. Her menses had ceased, with commencement of her present illness. She was admitted under the general surgery service. Physical examination revealed a thin built young woman, with extensive circumoral pustular lesions, and numerous scars of previous skin abscesses below her right breast and lower limbs. A few discrete lymph nodes were palpable in the neck. Vital signs showed a pulse of 90/minute, temperature of 38°C, blood pressure of 110/90 mmHg, and respiratory rate of 21 breaths/minute. Her weight was 32.2 kg, and her height was 160 cm. The abdominal exam showed a Kocher incision and multiple scars all over her abdomen, with tenderness in the right upper quadrant. Cardiovascular system examination revealed evidence of mitral regurgitation, with a systolic murmur grade of 3/6. Examination of the chest and central nervous system was normal. Urinalysis was normal. Laboratory results revealed white blood cells  $18 \times 10^9/l$  with neutrophilia of 78.6%, hemoglobin level 10.4 g/dl, mean red cell volume 74 fl, mean cell hemoglobin 24.2 pl, mean cell

hemoglobin concentration 32.6 g/dl, and a platelet count of  $376 \times 10^3$ . Erythrocyte sedimentation rate was 70 mm/hour. Renal profile showed: glucose 3.1 mmol/l, urea 1.22 mmol/l, creatinine  $39.75 \mu\text{mol/l}$ , sodium 136 mmol/l, potassium 3.9 mmol/l. The liver function tests showed: aspartate aminotransferase 19 u/l, alanine aminotransferase 20 u/l, alkaline phosphatase 111 u/l, total bilirubin  $3.61 \mu\text{mol/l}$ , and albumin 16.7 g/l. Coagulation profile revealed: prothrombin time 17.2 seconds, partial thromboplastin time 36.6 seconds, and an international normalized ratio of 1.24. Thyroid profile was normal. Human immunodeficiency virus screen, malaria films thick and thin, and a Mantoux test were all negative. Serology for *Brucella abortus* and *Brucella melitensis*, *echinococcosis*, and amebiasis were negative. An ultrasound of the abdomen revealed 2 multiloculated liver abscesses with collection in the left liver lobe measuring 5.5 x 8.5 x 12 cm, and right lobe collection measuring 3.5 x 3 cm.

The patient was admitted to our surgical unit, and underwent a computed tomography (CT) guided aspiration of a left liver lobe abscess, which drained 280 ml of frank pus, and a drain was left in situ (**Figure 1**). She was commenced on ceftriaxone 2 grams (gm) intravenously (iv) every 24 hours, and metronidazole 500 milligrams (mg) iv every 8 hours. On day 5 of hospitalization, she developed a left axillary abscess, which was aspirated. The following day she underwent a second CT guided aspiration of left lobe abscess. On the 9th day of admission cultures from both the liver and axillary abscesses reported *S.aureus* sensitive to oxacillin and flucloxacillin, and a 1.5 gm iv every 6 hours was added. On 12th and 16th days of

admission, she underwent 2 further attempts to drain her liver abscesses under CT guidance but to no avail, and with no defervescence of her fever. Flucloxacillin was changed to vancomycin 1 gm iv every hour, and ampicillin 500 mg iv every 6 hours. On the 29th day of admission, she remained febrile with temperature up to  $39.2^\circ\text{C}$ . A repeat CT scan showed right liver lobe abscess of 7 x 5 x 5 cm, and a left liver lobe abscess of 4 x 3 cm. Percutaneous needle aspiration under CT guidance yielded pus, which grew *S.aureus* sensitive to cloxacillin. Ceftriaxone, vancomycin, ampicillin, and metronidazole were discontinued and flucloxacillin was re-introduced at 1 gm iv every 4 hours. Actinomycoses stain of aspirate was reported negative. The patient developed a myoclonic seizure without a post-ictal period, no loss of sphincter control, and no up-going plantar response. Serum electrolytes were normal apart from magnesium 0.61 mmol/l (normal range = 0.6 - 0.35 mmol/l) on the lower side, which was corrected. The CT of the brain with contrast was normal. A trans-thoracic echocardiogram revealed evidence of rheumatic heart disease with grade III mitral regurgitation, and mild systolic dysfunction with no obvious vegetations. Following initial management with a benzodiazepine, she was commenced prophylactically on phenytoin, but continued to have seizure-like episodes despite adequate serum levels of phenytoin. Again, magnesium was found to be low at 0.49 mmol/l, and was corrected. She was transfused with 2 units of packed red blood cells when hemoglobin was found to be 7.5 gm/dl ( $13.7 \pm 1 \text{ gm/dl}$ ), and developed pulmonary edema on the following day, for which she was admitted to the intensive care unit. On day 36 of admission,



**Figure 1** - Computed tomography of the liver showing a hypodense lesion in left lobe, with subcutaneous extension.



**Figure 2** - The legs showing multiple scattered scars from repeated superficial infections.



**Figure 3** - The abdomen showing unhealed scars of laparotomies, and superficial scarring.



**Figure 4** - Computed tomography scan showing collapsed liver, and subcutaneous abscess cavity.

she was found to have a red macular lesion over her forearms, which were thought to be due to drug allergy. She had developed oral thrush, a cough productive of yellowish sputum, and complained of vaginal discharge. Nystatin mouthwash and co-trimoxazole pessaries were instituted. Cultures were taken where *Klebsiella pneumoniae* resistant to co-amoxiclav, cephalotin, cefoxitin but sensitive to ceftazidime was reported from the sputum culture, *Candida albicans* from the blood, and the vaginal swab showed culture of *Pseudomonas* species that are fully sensitive. She was commenced on ceftazidime 750 gm iv every 8 hours, amikacin, and oral fluconazole. A consultation on infectious diseases was made, and the condition of CGD was suspected on the basis of past and current history of liver abscesses, scars of recurrent subcutaneous abscesses on the breast and lower extremities, cultures positive for *S.aureus*, and the fact that there had been no abatement of fever despite drainage and adequate antibiotic therapy. The telltale lesions of previous infections on her lower extremities were pointed out (**Figure 2**). Nitro blue tetrazolium test was carried out in the Physiology department, King Saud University, Riyadh, KSA, and found to be positive. Further neutrophil function tests in the form of phagocytosis (respiratory burst), and phagocytic index (yeast uptake) were requested. These were performed and showed the absence of a phagocytic burst response on the whole blood and isolated polymorphonucleocyte (PMN) as compared to control, and her phagocytic index by yeast uptake isolated PMNs was weak (31%), as compared to control (61%). These results confirmed the diagnosis of CGD. Therapy with interferon  $\gamma$  1b 60  $\mu$ g subcutaneously 3 times/week was suggested along with cloxacillin 1 gm iv every 6 hours. However, the former could not be obtained by the family for financial reasons, and the surgeons decided to go for an operation

to debride the abscesses, which she underwent without complications (**Figure 3**). Multiple pockets of pus were ruptured in the right lobe of the liver and an abscess collection between the abdominal wall, and the left lobe of the liver was evacuated (**Figure 4**).

An ultrasound 4 days later showed yet another 2 unresolved abscesses in the right lobe of the liver. Despite this finding we opted to discharge her, on the 62nd day, on oral clindamycin 300 mg every 8 hours, for the next 6 weeks. On follow-up in the Infectious Disease clinic after one month, her symptoms had resolved and she was able to resume her normal daily activities. After completing the clindamycin course, she was commenced on trimethoprim-sulphamethoxazole, one double strength tablet (160/800 mg) every 12 hours, against recurrent bacterial infection. Eventually interferon  $\gamma$  was commenced, and her condition improved markedly with no further admissions, but the treating team was informed that she died in a tertiary care facility. The cause of death is not known to us, but presumably of an overwhelming infection.

**Discussion.** Chronic granulomatous disease is a rare inherited primary immunodeficiency disorder, in which phagocytes cannot dispose catalase-positive bacteria and fungi.<sup>2</sup> The absence of the respiratory burst and, hence, failure of destruction of the invading microorganism, leads to decreased intracellular killing of phagocytized microorganisms with consequent infections, which frequently turn into superficial and deep abscesses.<sup>2</sup> Hepatic abscesses are common, recurrent, and often multiple.<sup>2</sup> They develop due to the fact that the liver is a site of constant bacterial challenge.<sup>4</sup> Infectious complications often begin in infancy, and in those who survive into adulthood, the clinical course may be less severe.<sup>5</sup> Clinically, our

patient exhibited the manifestations commonly seen in CGD namely, liver abscess, circumoral dermatitis, and recurrent pyogenic cutaneous infections. Suppurative lymphadenitis, lung abscesses, pneumonia, subcutaneous abscesses, osteomyelitis, and blepharitis can also occur.<sup>5</sup> The diagnosis was delayed because the scars of recurrent cutaneous abscesses in the lower extremities were, at first, overlooked and the circumoral lesions were mistaken for severe acne, when eventually an infectious disease consultation brought the treating team on the right track by pointing out healed lesions of recurrent superficial skin infections in the patient's legs (**Figure 2**). The convulsion sustained by the patient during hospitalization, most likely, was due to antibiotic therapy since she had no previous epileptic history, no central nervous system abnormality, and with normal electrolytes apart from magnesium. Both flucloxacillin and ceftriaxone are known to be epileptogenic due to the beta-lactam ring in the former and a heterocyclic ring at position 3 and a heteroaromatic nucleus at position 7 of 7-aminocephalosporanic acid in the latter.<sup>6</sup> Diagnosis is readily made with a knowledge of the possible existence of the condition in an adult, the history of recurrent infections, the telltale multiple superficial infections with scarring with which the patient presents, and a test for respiratory burst and phagocytic index (yeast uptake), as in our case.<sup>5</sup>

The treatment strategies of hepatic abscesses due to CGD can be divided into non-invasive and invasive. Non-invasive therapy entails the prolonged administration of appropriate antibiotics according to the culture and sensitivity results, or with empiric therapy directed against *S.aureus* and gram-negative bacilli, if cultures are pending.<sup>5</sup> Interferon  $\gamma$  1b is the treatment option for acute liver abscesses and by boosting the body's defenses, can achieve healing in a matter of 3 months.<sup>7</sup> If interferon is not available and the patient is judged to be a poor surgical candidate, a granulocyte-macrophage colony stimulating factor can be instituted.<sup>8</sup> Percutaneous drainage of the abscess can be attempted and, if fails, can be combined with percutaneous trans-hepatic alcoholization of abscess cavity as mentioned in one report as an alternative to surgery.<sup>9</sup> Invasive treatment is purported by most of the

literature due to recurrence of abscesses after drainage and prolonged hospitalization, and is in the form of primary hepatic resection with removal of all tissues.<sup>2,4,5</sup> Prophylactic use of antimicrobial agents is an established practice in CGD, and usually consists of trimethoprim, sulfamethoxazole, however, we continued our patient on interferon  $\gamma$ . Itraconazole has shown to be an effective and well-tolerated treatment to reduce the frequency of fungal infections.<sup>1</sup> We conclude that a patient with CGD, nowadays, may survive into adulthood and a high index of suspicion will lead to a timely diagnosis in order to institute the appropriate therapy.

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