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Rapid Resolution of Multiple Liver Abscesses in a Chronic Granulomatous Disease Patient with Granulocyte Transfusions

Çoklu Karaciğer Apsesi Olan Bir Kronik Granülomatöz Hastasının Granülosit Transfüzyonu ile Hızlı Tedavisi

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ABSTRACT

Chronic granulomatous disease (CGD) is a genetically heterogeneous primary immune deficiency of phagocyte function characterized by recurrent, life-threatening bacterial and fungal infections that lead to granuloma formation. Early diagnosis is possible by the awareness of the clinician about early infectious clues of the disease. Aggressive treatment of infectious complications is very important in CGD patients and subsequently antimicrobial (antibiotic and antifungal) and immunomodulatory (interferon-gamma) prophylaxis until hematopoietic stem cell transplantation. Despite improved mortality, morbidities due to complications associated with CGD remain significant. One of these is a hepatic abscess in CGD patients which is seen in more than one-quarter of patients and also very refractory and frequently requires multiple surgeries with frequent morbidities. Therefore, the most optimal and beneficial treatments are still being investigated in the world. We present a 3 y old CGD patient with multiple liver abscesses due to *S.aureus* and *Aspergillus spp* who treated by several percutaneous liver-directed interventional radiological treatment along with granulocyte transfusions.

Key Words: Child, Granulomatous disease, Liver abscess

ÖZ

Kronik granülomatöz hastalık (CGD), tekrarlayan, yaşamı tehdit eden bakteri ve mantar enfeksiyonları ile karakterize olan, granülom oluşumuna yol açan genetik olarak heterojen bir primer immün yetmezlik olan fagosit fonksiyon yetersizliğidir. Erken teşhis, klinisyenin hastalığın erken enfeksiyon ipuçları konusunda bilinçlenmesi ile mümkündür. CGD hastalarında Enfeksiyöz komplikasyonların agresif tedavisi çok önemlidir ve hematopoietik kök hücre nakline kadar antimikrobiyal (antibiyotik ve antifungal) ve immünomodülatör (interferon-gama) profilaksileri de çok önemlidir. Mortalitenin azalmasına rağmen, CGD ile ilişkili komplikasyonlara bağlı morbiditeler önemini korumaktadır. Bunlardan biri, CGD hastasında, hastaların dörtte birinden fazlasında görülen ve aynı zamanda çok dirençli ve sıklıkla sık morbiditeli birden fazla ameliyat gerektiren karaciğer apsesidir. Bu nedenle dünyada halen en uygun ve faydalı tedaviler araştırılmaktadır. Granülosit transfüzyonları ile birlikte perkütan karaciğere yönelik girişimsel radyolojik tedavi ile tedavi edilen *S.aureus* ve *Aspergillus spp*'ye bağlı çoklu karaciğer apsesi olan 3 yaşında bir CGD hastasını sunuyoruz.

Anahtar Kelimeler: Çocuk, Granulomatöz hastalık, Karaciğer absesi

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INTRODUCTION

Chronic granulomatous disease (CGD) is caused by mutations leading to defects in subunits of the phagocyte NADPH-oxidase (gp91phox in X-inked; p22phox, p47phox, p67phox, and p40 in autosomal recessive-CGD) (1). The NADPH-oxidase-myeloperoxidase system generates microbicidal, reactive oxygen species required for host defense and control of inflammation (1).

CGD affects ~1:200 000 live births (2). X-linked-CGD accounts for approximately two-thirds of patients in Europe but in countries where consanguineous marriages are prevalent AR-CGD patients predominate (3-7). Symptoms comprise invasive infections and chronic autoinflammatory diseases (complications) leading to aggressive medical interventions, long hospitalizations, impaired quality of life, and increased morbidity/mortality (3-6) (Table I).

Infections typically affect organs in contact with the outside world like skin, gastrointestinal tract, and lungs as well as lymph nodes that drain these organs. Because of adjacent tissue and hematogeneous spread of the infection other organs can be affected especially the liver, bones, kidneys, and brain. Pathogens responsible for these clinical presentations are catalase-positive microorganisms as seen in Table I.

The use of life-long antibacterial prophylaxis with trimethoprim-sulfamethoxazole is recommended. Pulmonary Aspergillus infections are the leading cause of mortality. Anti-fungal prophylaxis mainly with itraconazole can reduce the incidence of fungal infections (1-3). One of the most serious errors in the management of CGD patients is the failure to treat potentially serious infections early and to continue therapy long enough to eradicate them.

Although neutrophil absolute numbers are normal in CGD patients, it can be considered functional neutropenia because the killing function is impaired. Granulocyte transfusions have been used to treat infections in neutropenic patients for nearly 30 years (8-10) (Table II). The data from recent systematic reviews suggest that properly collected and promptly infused granulocytes are active against bacterial and fungal infections in the patient. The most important question is in which patients the administration of granulocytes will be necessary. Prominent evidence suggests that granulocyte transfusions should be used in selected cases, as a final measure to control an infection that is expected to be refractory to optimal antimicrobial treatment.

In this regard, CGD patients who do not have their neutrophil response to the infection are good candidates for granulocyte transfusions (Table II).

It was planned to present our CGD patient with multiple liver abscesses to emphasize the characteristics of the use of granulocyte transfusion, which is a rare treatment method, the infection in CGD patients is usually due to resistant microorganisms, which are not common in the society, and its proven benefit in organ abscesses and rapidly spreading skin infections.

Table I: Infections, chronic complications, and organisms responsible in CGD patients in order of frequency.

INFECTIONS	CHRONIC COMPLICATIONS	INFECTING ORGANISMS
Pneumonia	Lymphadenopathy	*Staphylococcus aureus*
Lymphadenitis	Hypergammaglobulinemia	*Escherichia coli*
Cutaneous infection-impetigo	Hepatosplenomegaly	*Aspergillus species*
Hepatic-perihepatic abscess	splenomegaly	*Salmonella species*
Osteomyelitis	Anemia of chronic infection	*Klebsiella species*
Septicemia	Underweight	*Burkholderia cepacia*
Otitis media	Short stature	*Staphylococcus epidermidis*
Conjunctivitis	Chronic diarrhea(Crohn-like)	*Serratia marcescens*
Enteric infections	Gingivitis	*Enterobacter species*
Urinary tract infections	Dermatitis	*Streptococcus species*
Sinusitis	Chorioretinitis	*Proteus species*
Renal-perinephric abscess	Hydronephrosis	*Candida species*
Brain abscess	Ulcerative stomatitis	*Nocardia species*
Pericarditis	Pulmonary fibrosis	*Bacillus Calmette-Guérin*
Meningitis	Esophagitis	*Mycobacterium species*
	Gastric antral narrowing	*Chromobacterim violaceum*
	Granulomatous ileocolitis	*Candida glabrata*
	Granulomatous cystitis	*Actinomyces*
	Discoid lupus erythematosus	*Granulibacter bethesdensis*

Table II. Indications of granulocyte transfusions.

Minimal criteria:
Absolute neutrophil count<500/mm^3
Evidence of bacterial or fungal infection
Unresponsiveness to antimicrobial treatment for at least 48 hours
Cancer patients with severe neutropenia and fatal infections
Chemotherapy or HSCT-induced neutropenia
Aplastic Anemia
Congenital disorders of neutrophil function (Leucocyte Adhesion Deficiencies, Congenital Severe Neutropenia syndromes, Chronic Granulomatous Disease)

CASE REPORT

A 3 y old male patient from a Syrian immigrant family, admitted first when he was 18 mo old, to the Republic of Turkey, Ministry of Health, Ankara City Hospital, Children's Hospital, Emergency Department with a complaint of scrotal swelling. On admission, there was a left apical cervical, 1.5x1.5 cm diameter lymphadenopathy, submandibular pigmented scars left due to previous suppurative lymphadenitis, hepatomegaly 1 cm below the costal margin, palpable left inguinal lymphadenopathy, multiple micro epididymal, and scrotal abscess. His weight was 10 kg. The patient consulted the Pediatric Immunology Unit for primary immunodeficiency diseases and especially for congenital defects of phagocyte number and functional defects due to the skin and soft tissue infections of the patient. Parents were first-degree relatives (cousins). The patient was the 1st child of the family, and 2nd child was 7 mo old and healthy. There was a perianal abscess in the newborn period in his history. He was hospitalized and the biopsy of the cervical lymph node was reported as necrotizing granulomatous inflammation by the pathologist. The patient was evaluated with the immunological screening tests as seen in Table III. Nitroblue tetrazolium test showed the killing defect of the neutrophils of the patient and the Dihidro-rhodamine 123 test showed that the patient's probable mutant NADPH-oxidase component is p67 phox protein according to the stimulation index found. Mutation analysis results are pending for the precise diagnosis. After antimicrobial treatment, he was given the drug reports and prescriptions of prophylactic TMP-SMX 5mg/kg/d, 3 days/week, per oral.; itraconazole 5mg/kg/d, every day, per oral., and interferon-gamma (Imukin® -1b 100mcg flacon) 3 days/week, sc. and called for Pediatric Immunology outpatient clinic controls. Since the patient had a routine BCG vaccine, no history of BCGitis, a PPD test was applied. Since the result was 18 mm, chest radiography and CT were taken due to the possibility of active TB infection. It was normal; prophylactic Isoniazid and Rifampicin treatments (both 10 mg/kg/d dose) were started for latent TB. The family belonged to a low socio-cultural level and could bring the child 12 months later for the new complaints of the child. They stated that they could not give the TMP-SMX, itraconazole continuously and regularly, except prophylactic TB drugs. Since the family was a Sirian immigrant, we contacted Sirian Social Aid Organisations in Turkey but Imukin could not be provided. His current complaints were >38° C fever of 5 days, abdominal pain, severe weakness, and pallor. The patient was hospitalized again in 2020 October. Physical examination revealed oral moniliasis, abdominal distention, bilateral suppurative cervical lymphadenitis with 3x3 cm diameter. Laboratuary tests were given in Table III. Abdominal USG and abdominal MRI revealed multiple (nearly 8-9) subcapsular and scattered abscesses the biggest ones sized 42x48, 28x20, and 34x27 mm diameter at the right lobe of the liver. There were another abscess sized 23x17 adjacent to the upper part of the right kidney with an undetectable capsular border. There were also multiple reactive mesentery lymphadenopathies and minimal free liquid collection. Computed tomography of the thorax showed no appearance in favor of pulmonary TB and Aspergillus pneumonia when compared with previous MR, but 18 mm right pleural effusion. Cranial MRI was normal. Treatment began with meropenem, vancomycin, teicoplanin, amikacin, and caspofungin. IVIG was added as a single dose to support the treatment in a 0.5g/kg/dose. Subcapsular hepatic abscesses drained percutaneously. Despite these treatments, fever, blood, and abscess culture yields of *S.capitis* in the blood; *Aspergillus spp*. and *Staphylococcus spp* in the hepatic abscess respectively, and the high number of the abscesses led us to decide to give granulocyte transfusion (GTX) to the patient. After the 14th day, vancomycin and caspofungin stopped and voriconazole was begun. After GTXs and multiple (3 times) interventional abscess drainages until they solidify, he remained afebrile, imaging showed improvement of all the abscesses, and the return of the erythrocyte sedimentation rate to its normal baseline (<20mm/h), the patient could be discharged after 1.5 months of antibiotic and antifungal treatment, returning to the routine CGD prophylaxis and increasing the awareness of the family about CGD, the decision was made to prepare for bone marrow transplantation. The patient was also discharged with continuing voriconazole treatment.

DISCUSSION

Recurrent cutaneous abscesses and lymphadenitis represent the earliest and common types of infection in CGD as seen in our patient. İmpetigo, froncules frequently in the perianal area due to feces contamination as well as recurrent perirectal abscess are seen (Table I). These require prolonged courses of oral and topical antibiotics to clear and once formed can persist for years despite aggressive antimicrobial treatment.

Hepatic and perihepatic abscesses were also quite common in CGD as seen in our patient, mostly caused by the hematogenous spread of *S.aureus* in patients who are incompatible with

Table III: Immunological screening tests and other laboratory parameters of the patient on the two admissions.

	First admission	Second admission
CBC		
WBC	3930	18770
ANC	2000	12770
ALC	1100	4830
Plt	728 000	774 000
Hb/Hct	12.5/36	9/27
Eosinophil(%/Absolute)	12 (471)	1(200)
Serum immunoglobulins(mg/dl)		
IgG	1550	
IgM	250	
IgA	155	
IgE (U/ml)	500	
Lymphocyte subpopulations		
CD3+ Total Tcell(%/Absolute)	65	
CD4+Helper T cell (%/Absolute)	37	
CD8+ supressor T cell(%/Absolute)	25	
CD19+ B cell(%/Absolute)	26	
CD16+56 NK cell (%)	9	
Nitroblue Tetrazolium Test (NBT)	0%	
Dihidro-rhodamine 123 test	P67phox mutation is possible according to the pattern.	
Complement (mg/dl)		
C3	100	
C4	30	
CRP/Sedimentation on admission	3 mg/dl; 75mm/h	12,7 mg/dl; 100mm/h
The isolated pathogen in culture	*S. aureus*	*S. aureus*+ *Aspergillus spp*
Liver/ Renal function tests	Normal limits	Normal limits
Coagulation tests(PT, PTT, D-dimer, Fibrinogen, Ferritin)	Normal	High

the prophylactic treatment. Spontaneous rupture can be seen, again as seen in our patient. Liver function tests are often normal. Hepatic abscesses in CGD are phenotypically distinct from the pyogenic liver abscesses associated with other conditions. They present as septate masses surrounded by a thick pseudocapsule containing amorphous cell debris in it which is difficult to drain. The resolution requires open surgical drainage or excision of the lesion (other surgical procedures may also be necessary such as liver resection, segmentectomy, or lobectomy); percutaneous interventional radiological procedures, and high dose corticosteroid use together with several months of targetted parenteral antibiotics (8,9). It is hypothesized that steroid-induced reduction of systemic inflammation reduces immune cell infiltration in the liver microenvironment and so reduces the need for procedural intervention and prevents complications. Corticosteroids (prednisone or methylprednisolone) as immunomodulatory management are used in a median dose of 1 mg/kg/day and subsequently tapered over a median of 5 months (8,9).

In recent years the prognosis of these organ abscesses has dramatically improved with the use of GTX. In cases of severe fungal and bacterial infections that fail to respond to medical and surgical approaches, GTX is necessary to shorten the healing process.

We have experience with GTX in our hospital in severe necrotizing pneumonia, Aspergillus pneumonia, cerebral and cerebellum abscesses, osteomyelitis, and liver abscess in at least ten X- and AR-CGD patients to date. We observed its effectiveness in curing infections in CGD patients. We gave GTX also to this patient once in three days, from 4 unrelated donors with only one transfusion reaction of fever in the last infusion. Due to this reaction, the last GTX had to be cut in the half. He received high-dose granulocyte per body weight (Weight: 10 kg) since each granulocyte products contained 2.9 x1010, 1.4 x1010, 1.2 x1010 and 1.5 x1010 neutrophils respectively. We did not prefer steroid use in this patient because the patient's cultures obtained from drainage procedures were positive for *Aspergillus spp* and the danger of spread could be increased with steroids.

The Apheresis Unit of our hospital has a well-established granulocyte donor and patient preparation protocol for donor selection, viral screening, time and amount of G-CSF and dexamethasone doses are given to the donor, apheresis procedure (time to obtain the largest amount of granulocytes),

premedications given to the patient, and infusion rates (transfusing the product within 8 hours). We did not see any severe adverse reaction after GTX in our CGD patients, while some patients develop hypoxemia and pulmonary infiltrates after GTX with a frequency of 10% in some CGD patient trials (10,11).

There is another issue to be considered in CGD. Special attention must be given to CGD patients' transfusions, whether they be GTX, erythrocytes, or platelets (1,2). Some X-CGD patients have McLeod syndrome. Since the Kx protein is absent and other Kell antigens are weakly expressed on erythrocytes of X-CGD patients, they will become quickly sensitized to the Kell antigens if they are not transfused with Kx-negative McLeod blood products. If the molecular genetic basis of the CGD patient is not known erythrocyte antigen phenotyping should be studied before the first transfusion of the CGD patient because it is not possible to prevent red blood cell contamination during the apheresis procedure. Our patient's Kell blood group phenotyping was negative.

However, GTX often leads to alloimmunization which may significantly impair the likelihood of successfull hematopoietic stem cell transplantation later on. Thus because of the increasing desire for HSCT in CGD, we reserve GTX for severe complications and use unrelated donors only in our patients. HLA and neutrophil alloimmunization in CGD patients who received frequent GTX in a study was 70% (14/18) (12).

To conclude, hepatic abscesses occurring in patients with CGD represent a clinically significant and life-threatening complication. GTX's may be life-saving and time-saving for the patient since evidence reveals that these lesions respond quickly to viable granulocytes to overcome the immunodeficient immune system of the CGD patients.

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