Case Number 4
Chronic Granulomatous Disease (CGD)

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Case summary:

Demographic details:

Ms. CC, female, Rabat.
Referred from: Hospital.

An 8-year old girl presented with a 2-year history of recurrent nasal skin infections. In this context of a prolonged history of facial and nasal infections, multiple perianal abscesses and a non-specific chronic colitis, an underlying immunodeficiency was suspected. She was referred for further immunological assessment and after ruling out other haematological disorders, the diagnosis of Chronic Granulomatous Disease (CGD) was made following an abnormal Nitroblue Tetrazolium (NBT) test. The patient was started on long-term prophylactic antibiotics and genetic testing is currently being carried out on her family. Bone marrow transplantation is the optimum treatment but will only be considered when the benefits outweigh the risks.

Presenting complaint:

Repeated nasal skin infections – 2 years.

History of presenting complaint:

The patient has been suffering from recurrent nasal skin infections for the past two years which, despite response to co-amoxiclav, merited referral to hospital. She complains of nasal congestion and purulent discharge. She also has associated excoriation and crusting of the nose. On one occasion, chronic herpes simplex virus infection was suspected but there was no improvement on treatment with acyclovir. Similar episodes occurred before the age of four some of which were associated with aphthous ulceration of the mouth.

Past medical and surgical history:

Past medical history:

Nasal furunculosis – 6 months of age
Maxillary sinusitis and facial cellulitis treated with intravenous antibiotics – 4 years of age
Nasal vestibulitis treated with intravenous antibiotics – 6 years of age
Pustule on left palm – 7 years of age

Past surgical history:

Incision and drainage of several perianal abscesses – 6 years of age
Sigmoidoscopy + rectal biopsy – 6 years of age
Colonoscopy + multiple biopsies suggesting mild chronic non-specific colitis without Crohn's abscesses – 7 years of age

Drug history:

Co-amoxiclav

No known drug allergies.

Family history:

The parents are unrelated and currently well.
Her father has suffered from a chronic skin ulceration over both knees but has no other major illnesses.
Her 9-year-old brother is well and there are no significant illnesses in any other family member.

Social history:

The patient lives with her parents and older brother. She goes to school and interacts well with her peers.

Systemic inquiry:

- General Health: Feeling well in general. Afebrile.
- Cardiovascular System: Nil to note.
- Respiratory System: Nil to note.
- Gastrointestinal System: Nil to note.
- Genitourinary System: Nil to note.
- Central Nervous System: Nil to note.
- Musculoskeletal System: Nil to note.
- Endocrine System: Nil to note.
- Others: Nil to note.

Current therapy:

Ciprofloxacin 250mg bd – to treat nasal infection due to staphylococcus and streptococcus.
Rifampicin 300mg bd – to treat nasal infection due to staphylococcus and streptococcus.

Discussion of results of general and specific examinations:

General examination:

Admission weight: 27.3kg (60th centile)
Admission height: 133cm (80th centile)
Blood pressure: 100/60 mmHg

There is moderate submandibular lymphadenopathy.

Specific examinations:

Examination of the cardiovascular and respiratory systems was unremarkable. Heart sounds were normal and the chest was clear. Abdominal examination showed a soft non-tender abdomen and no hepatosplenomegaly. Neurological examination was normal as were the ears and throat. The patient has a markedly inflamed nose with crusting and occlusion of the nares.

The lymphadenopathy and nasal inflammation point towards an upper respiratory tract infection. The rest

of the examination was unremarkable indicating that the infection has remained localised and no other system has been affected.

Differential diagnosis:[1,2]

- Common variable immunodeficiency
- Inflammatory bowel disease
- Myeloperoxidase deficiency
- Severe combined immunodeficiency
- Autoimmune neutropenia
- Hyperimmunoglobulinaemia E syndrome
- Infection with Mycobacterium tuberculosis
- Primary immunodeficiency
- Impetigo
- Sarcoidosis
- Seborrhoeic dermatitis
- Glucose-6-phosphate dehydrogenase deficiency (G6PD)
- Childhood HIV disease
- Eosinophilic pustular folliculitis
- Leukocyte adhesion deficiency type I
- Wiskott-Aldrich syndrome

Diagnostic procedures:

Laboratory exams:

Test: Full blood count.
Justification for test: Screening for anaemia, acute or chronic infection, thrombocytopenia and any haematological disease.
Result: Hb – 12.7g/L
WCC – 5.9 x 109/L
Platelet count – 139 x 109/L
Conclusion: No anaemia present. WCC within normal values suggesting a more chronic course of infection and no neutropaenic cause. Mild thrombocytopenia non-specific.

Test: Urea and electrolytes.
Justification for test: Baseline values.
Result: Normal.
Conclusion: No electrolyte disturbance or acute renal dysfunction.

Test: LFTs.
Justification for test: Liver has a tendency to become infected in immunodeficiency and form abscesses.
Result: Normal bilirubin, alkaline phosphatase and alanine transaminase.
Conclusion: No hepatic dysfunction.

Test: Nasal culture and sensitivity.
Justification for test: Isolation of causal micro-organism.
Result: Presence of Staphylococcus aureus and group G beta-haemolytic streptococci sensitive to flucloxacillin and ampicillin.
Conclusion: Staphylococcus cultured but no other opportunistic pathogens present.

Test: Nitroblue tetrazolium (NBT).
Justification for test: Screening for chronic granulomatous disease.
Result: Zero reduction of the dye.
Conclusion: Result is consistent with chronic granulomatous disease.

Test: G6PD screen.
Justification for test: Screening for possible homozygous G6PD giving CGD phenotype.
Result: Normal.
Conclusion: Exclusion of G6PD.

Test: Autoimmune screen.
Justification for test: Screening for systemic lupus erythematosus.
Result: Anti-nuclear factor, rheumatoid factor and anti-neutrophil cytoplasmic antibodies were all negative. Anti-cardiolipin antibodies were mildly elevated.
Conclusion: No autoimmune diseases suggested.

Test: Miscellaneous.
Justification for test: To rule out specific haematological diseases.
Result: Immunoglobulins, neutrophil chemotaxis and CD18 expression were all normal.
Conclusion: There is no hypogammaglobulinaemia, neutropaenic disorders and leukocyte adhesion deficiency respectively.

Instrumental exams:

Test: Chest X-ray.
Justification for test: Screening for lung infections, abscesses and especially TB.
Result: Normal.
Conclusion: No lower respiratory chest infections or abscesses detected.

Test: Sinus X-ray.
Justification for test: Surveying the extent of infection.
Result: Moderate mucosal thickening in both antra.
Conclusion: Presence of chronic infection.

Therapy:[3]

Drugs:

Drug	Dosage	Frequency	Type	Reason
Ciprofloxacin	250mg	BD	Fluoroquinolone antibiotic	Treatment of infection
Rifampicin	300mg	BD	Rifamycin antibiotic	Treatment of infection

Diagnosis:

The history of recurrent infections coupled with an abnormal NBT test confirms the diagnosis of chronic granulomatous disease (CGD). Although full genetic analysis has not yet been carried out, CC is probably suffering from the autosomal recessive form of the disease due to an unremarkable family history to date.

Chronic granulomatous disease (CGD), also known as Bridges-Good syndrome, consists of a heterogenous group of disorders characterised by mutations in genes coding for different subunits of phagocyte NADPH oxidase. In normal individuals, this enzyme catalyses the transfer of electrons from NADPH

to oxygen resulting in formation of the superoxide anion, the first step in the production of reactive oxygen species (ROS) necessary for physiological phagocytic killing of bacteria and fungi. The failure to produce the superoxide anion and downstream antimicrobial oxidant metabolites makes the CGD patient susceptible to severe, life-threatening bacterial and fungal infections and excessive inflammation leading to granuloma formation[4]. Mutations can occur in one of at least 5 different genes involved in the assembly and activation of NADPH oxidase. The gene coding for the enzymatic centre, gp91phox is found on the X-chromosome and accounts for about two-thirds of cases. Autosomal forms occur, in descending order of frequency, from mutations in p47phox, p67phox, p22phox and p40phox, all subunits of the enzyme. X-linked CGD patients (gp91phox deficient) are most severely affected. CGD affects 1 in 200,000 persons worldwide[5].

CGD typically presents in early childhood with sinopulmonary infections, skin and organ abscesses, lymphadenitis or a general failure to thrive. In the absence of a known immunodeficiency, specific opportunistic infections caused by organisms such as Staphylococcus aureus, Burkholderia cepacia, Serratia marcescens, Nocardia species and Aspergillus species should increase the suspicion of CGD[6]. Inflammatory disorders such as inflammatory bowel disease at an early age and granulomatous cystitis can also be manifestations of CGD[4]. A family history of males with severe or recurrent infections could point towards the diagnosis of X-linked CGD whereas consanguineous parents increase the risk for the autosomal recessive form. In this young patient, severe infection of the face, recurrent sinus infection and perianal abscesses point towards an immunodeficiency of possible genetic origin such as CGD. The colonoscopy and biopsy findings of a Crohn's-like colitis further reinforce the diagnosis. An unremarkable family history and her female gender suggest against X-linked CGD in favour of the autosomal recessive type.

Being a rare disease, other primary immunodeficiency disorders were excluded before a diagnosis of CGD was strongly suspected. Hypogammaglobulinaemia, neutropaenic disorders and leukocyte adhesion deficiency were all tested for and excluded. The diagnosis of CGD requires demonstration of defective NADPH oxidase activity in neutrophils. The two most common diagnostic assays are the nitroblue tetrazolium (NBT) test and the dihydrorhodamine (DHR) test, the former being the easier to perform. It depends upon direct reduction of NBT to insoluble blue formazan by NADPH oxidase. Lack of NADPH activity, as happens in CGD, gives a negative result (no blue colour change). The DHR test involves staining whole blood with dihydrorhodamine and stimulating it to produce superoxide radicals which oxidize DHR to the fluorescent dye rhodamine in cells with normal function. A negative result seen in flow cytometry indicates a defect in PHOX enzymes[7] (Figure 1). Females who are homozygous for the genetic mutation causing glucose-6-phosphate dehydrogenase deficiency (G6PD) have reduced NADPH levels and therefore, can present phenotypically with CGD. This was excluded in the patient by means of a G6PD screen[8]. Zero reduction of the nitroblue tetrazolium in this case therefore confirmed the diagnosis of chronic granulomatous disease.

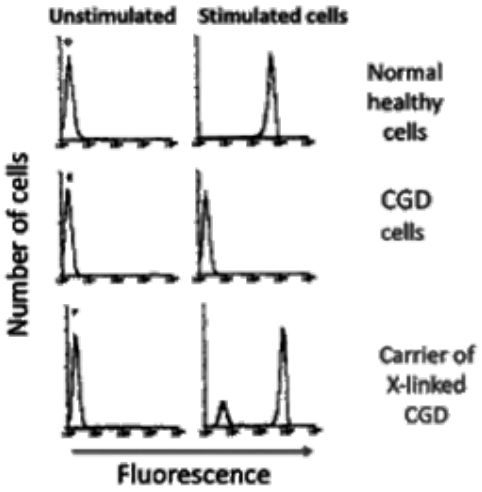

Figure 1:The DHR test for diagnosis of chronic granulomatous disease[9].

Final treatment and follow ups:

Ciprofloxacin and rifampicin were continued for 2 weeks, after which rifampicin was stopped and ciprofloxacin was changed to flucloxacillin 250mg qds together with co-trimoxazole 480mg bd. These were continued for a further 2 months for complete eradication of the current infection.

Long-term prophylactic co-trimoxazole and itraconazole were also initiated to prevent bacterial and aspergillus infections respectively. Itraconazole should only be taken if the frequency of infections starts to increase as the benefits of continual anti-fungal therapy are outweighed by the risks. In view of the fact that she has largely suffered from staphylococcal infections, measures to reduce staphylococcal carriage with application of mupirocin to her anterior nares and regular dusting with hexachlorophene powder should be used. An antiseptic shower wash should also be used for bathing.

Should the patient suffer from new infections or have a recurrence of her current problem, early and aggressive antibiotic treatment should be administered utilising an intravenous antibiotic if necessary. Some studies have shown that treatment with gamma interferon decreases the risks of invasive bacterial infections in patients with CGD.

The patient and her mother are currently undergoing full phenotypic and genotypic analysis to establish the form of inheritance of the disorder. The parents will then receive genetic counselling. Genetic testing for the patient's brother is also being taken into account.

The optimum treatment for a patient with CGD is a bone marrow transplant which will be considered as an option if the disease increases significantly in severity.

Fact Box 4:

Title: Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is an inherited immunodeficiency caused by defects in the NADPH oxidase complex responsible for producing the superoxide anion necessary for physiological killing of bacteria and fungi. This predisposes the individual to severe, life-threatening infections, excessive granulomatous inflammation and autoimmune diseases.

Risk factors

- Parents carrying the recessive trait
- Male sex in the X-linked type
- Female sex in the recessive type[10]

Symptoms

- Frequent skin infections that are difficult to treat
- Persistent diarrhoea
- Failure to thrive
- Bone pain
- Joint pain[10]

Signs

- Pyrexia
- Lymphadenopathy
- Hepatomegaly
- Splenomegaly
- Signs of pneumonia
- Furuncles
- Signs of cellulitis and impetigo[10]
- Atypical childhood infections eg. osteomyelitis, hepatic abscesses, especially if recurrent

Prevention

CGD cannot be prevented but prophylactic antibiotics and antifungals can be given to minimise the number and severity of infectious complications. Genetic counselling may also have a role in affected families[10].

Complications

- Sinopulmonary: pneumonia, upper respiratory tract infections, lung abscesses
- Dermatological: abscesses, furunculosis, impetigo, eczema
- Lymphadenitis
- Gastrointestinal: gastroenteritis, perianal abscesses and fistulae, gingivitis, granulomatous ileocolitis, stomatitis, gastric outlet obstruction
- Hepatobiliary: liver abscesses or granuloma
- Musculoskeletal: osteomyelitis, septic arthritis
- Neurological: meningitis, brain abscesses
- Urinary: lower urinary tract infections, pyelonephritis
- Haematological: septicaemia, anaemia[5, 11]

Prognosis:

There are currently no studies reviewing the long-term prognosis of CGD with modern treatment. Children without treatment die in the first decade of life, the commonest causes being bacterial or Aspergillus pneumonia and septicaemia. The X-linked type carries a worse prognosis than the autosomal recessive type with median survival time being 37.8 and 49.6 years respectively[11].

Treatment:

The mainstay of treatment is antibiotic prophylaxis with trimethoprim/sulfamethoxazole (co-trimoxazole), ciprofloxacin, clindamycin or rifampicin. Fungal prophylaxis with itraconazole is also recommended. Interferon gamma delivered by subcutaneous injection up to 3 times a week is useful in a few patients. Granulocyte infusions are increasingly given to CGD patients when traditional therapies fail to resolve severe, life-threatening infections, especially with *Aspergillus spp*. Stem-cell transplantation is associated with a significant risk of morbidity and mortality but is curative[12].

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