

## CLINICOPATHOLOGICAL CASE

### Infant with intestinal subocclusion syndrome associated with chronic granulomatous disease

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#### CLINICAL HISTORY SUMMARY (A-09-01)

A 5-month-old male patient attended outpatient consultation because of reduced evacuations with mucus and blood and with fever of 38-39°C.

#### Family History

The patient's mother is a healthy 17-year-old housewife who did not complete high school. The father is a healthy 21-year-old laborer who completed high school. There is no history of consanguinity.

#### Nonpathological History

Both parents are natives of a small community in the State of Mexico. They live in a house with four rooms. The patient was exclusively breastfed until 2 days prior to admission when formula was indicated. Psychomotor development was according to age. The patient received the following immunization scheme: bacillus-Calmette-Guerin (BCG) at birth, two dosages against hepatitis B, acellular 5-in-1 vaccine (diphtheria, pertussis, tetanus, *Haemophilus influenzae* type-B and poliomyelitis), oral

Sabin and 7-in-1 conjugated antipneumococcal vaccine including rotavirus.

#### Perinatal and Pathological Antecedents

The infant was the product of a first pregnancy. The mother attended prenatal care regularly, and the newborn was delivered through Caesarean procedure at a local hospital. The infant cried and breathed at birth. He had a birth weight of 3700 g, length 54 cm, and unknown Apgar score. The infant was discharged with his mother.

#### Current Illness

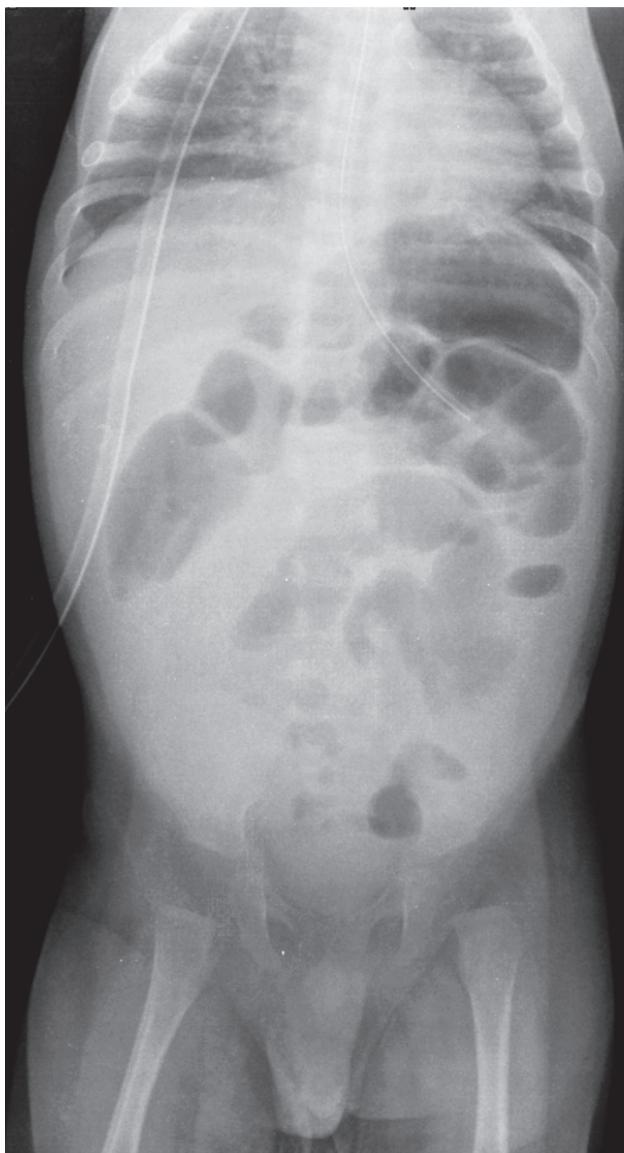
The patient was admitted first for 4 days after 3 days of illness with fever that reached 39.5°C. He was irritable, presented up to five greenish-colored evacuations per day with reduced consistency and without mucus or blood. He had biliary vomiting and progressive abdominal distention with 24 h evolution. The patient was referred to a second-level hospital. He was managed using paracetamol and metoclopramide without improvement and because of this was referred to our institution. Upon physical examination the patient presented the following: tachycardia, no fever, normotensive, pale, crying without tears, and distended and painful abdomen with reduced peristalsis. Abdominal x-ray showed dilation of intestinal loops and inappropriate air distribution (Figure 1). Acidosis was corrected and dehydration was managed using crystalloid fluid replacement. The patient was administered ampicillin-amikacin and was kept under observation and fasting. Because of clinical improvement, he was discharged with a 10-day course of antibiotic therapy.

Due to persistence of the patient's clinical profile, he was admitted to a private hospital on the same day that he was discharged from our institution where he was found to be pale, irritable with abdominal distension and absent

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**Figure 1.** Abdominal x-ray (November 10, 2008) from first admission. We observe poor gas distribution at intestine, hepatomegaly, and soft tissue and bones without alterations.

peristalsis. Abdominal x-ray revealed air-fluid levels and edema. A laparotomy with ileostomy was performed, demonstrating a regional lymph node with increased volume. Biopsy reported a granulomatous inflammation compatible with serous tuberculosis of the small intestine. Therefore, the patient was managed with rifampicin, isoniazid, pyrazinamide, teicoplanin and amikacin. Clinical evolution was torpid. The patient remained irritable with abdominal distension, fever and serous liquid leakage through the

surgical wound. Therefore, his mother requested voluntary discharge and returned once again to our hospital.

At the beginning of the second admission, physical examination revealed a 6000 g weight, 64 cm height, tachycardia, tachypnea, 36°C temperature, normotense. Abdomen was distended and painful upon palpation, stoma was without alterations and there was reduced peristalsis without other relevant alterations. Laboratory test results are shown in Table 1.

Abdominal x-ray revealed centralized intestinal loops with abundant fluid and without air-fluid levels or air in cavity (Figure 2). Patient was managed with fasting, base intravenous solutions and replacement of intestinal loss through stoma with crystalloid fluids. Infectology suspended antituberculosis drugs and initiated piperacillin/tazobactam, amikacin and vancomycin.

During the second hospitalization day, the patient presented hemodynamic deterioration and was managed with fluid containing crystalloids, colloids and dobutamine. He was moved to the intensive care unit. Surgical service placed a 3/8 Penrose drain at the left iliac fossa and right parietocolic groove, draining 200 mL of exudative effusion. During the third day of hospitalization, central cultures with abundant yeasts were found; therefore, central catheter was removed and amphotericin B/imipenem therapy was started and continued with vancomycin. Further hemodynamic deterioration took place with hypotension. Pathology Service reviewed biopsy sections taken at the private hospital and found the following: small intestine presented acute and chronic peritonitis, lymph node with chronic granulomatous lymphadenitis and connective tissue with chronic granulomatous necrotic inflammation. No microorganisms were grown.

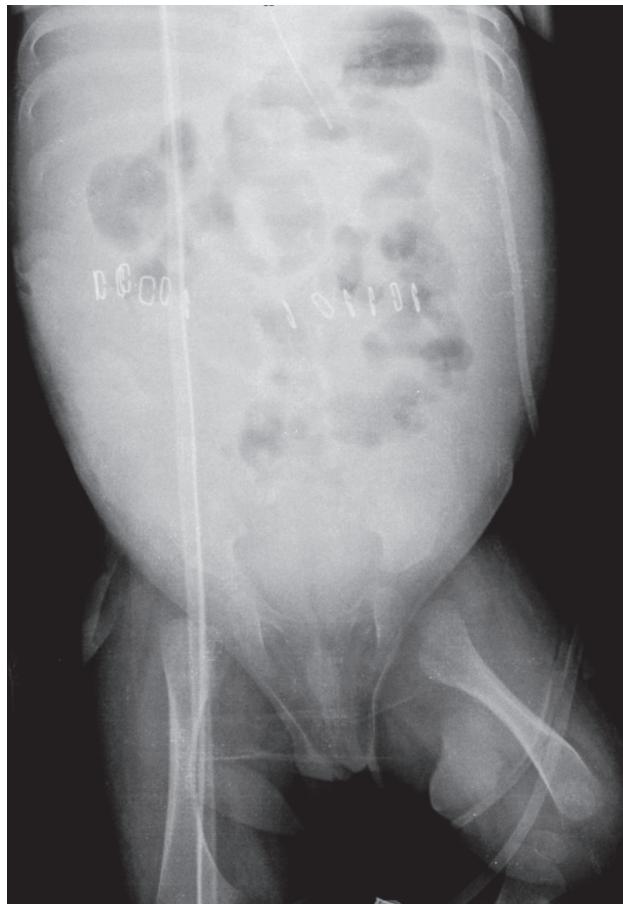
Between the 4<sup>th</sup> and 6<sup>th</sup> hospitalization day, the patient presented clinical and laboratory data compatible with disseminated intravascular coagulation (DIC) and received transfusions of packed red cells, frozen fresh plasma and cryoprecipitates. High-frequency mechanical ventilation was started together with total parenteral nutrition (TPN). Computed axial tomography (CAT) of paranasal sinuses reported occupation of maxillary sinuses and ethmoidal cells, chest CAT revealed bilateral basal consolidation, abdominal CAT revealed thickening of small intestine loops and free fluid in abdominal cavity (Figure 3).

Between the 8<sup>th</sup> and 14<sup>th</sup> hospitalization day, the patient presented persistent fever and intestinal fistula with biliary

**Table 1.** Relevant laboratory test results during hospitalization

Hg	Hct	Leu	Neu	Lc	PL	PT	PTT	Na	K	Cl
9.9 g/dl	26.7%	36,500/mm <sup>3</sup>	24,090	11,680	326,000	14 sec	25.3 sec	139 mEq/l	5.6 mEq/l	86.5 mEq/l
Alb	TP	IgG	IgM	IgA	IgE	C3	C4	HIV ELISA (mother)		
1.6 g/dl	4.9 g/dl	684 mg/dL	93.6 mg/dL	97 mg/dL	128 U/mL	37.2 mg/dL	16.9 mg/dL	Negative		

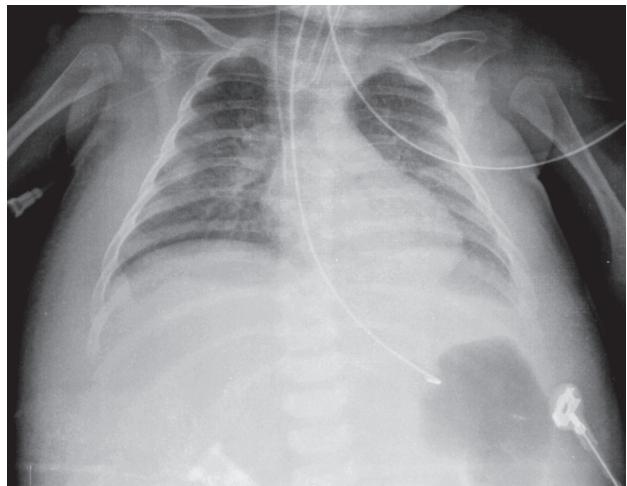
Hg, hemoglobin; Hct, hematocrit; Leu, leukocytes; Neu, neutrophils; Lc, lymphocytes; PL, platelets; PT, prothrombin time; PTT, partial thromboplastin time; Alb, albumin; TP, total proteins; IgG, IgM, IgA, IgE, immunoglobulins G, M, A, E; C3, C4, complement factors 3 and 4.



**Figure 2.** Abdominal x-ray (November 24, 2008) from the second admission. We observe distended abdomen with centralized intestinal loops, surgical staples at epi-mesogastrum. Image suggestive of intra-abdominal fluid.

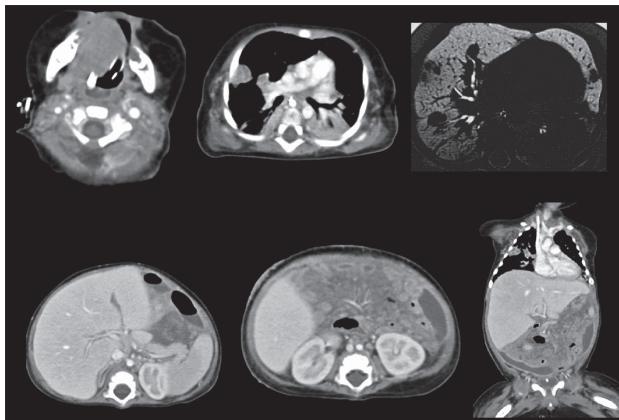
expense despite broad spectrum antibiotics and the use of vasoactive amines (milrinone and norepinephrine).

Between the 15<sup>th</sup> and 25<sup>th</sup> hospitalization day, the patient presented a torpid evolution with respiratory deterioration,



**Figure 3.** Chest x-ray (8th day of hospitalization) where we observe restrictive thorax due to hepatomegaly and abdominal cavity fluid and edematous soft tissues. Pulmonary fields present bilateral grid-node predominantly on right parahilar and apical regions.

tachypnea, fever, cutis marmorata and surgical wound dehiscence as well as exit of biliary material and small intestine loops. Abdominal CAT scan with contrast agent revealed increased mesenteric density and free fluid in the pelvic cavity (Figure 4). Exploratory laparotomy was carried out revealing multiple perforations in the small intestine and mesentery with 0.5-cm diameter lymph nodes. Debridement was carried out and the perforated segment was resected; gastrostomy and biopsies were carried out. On the days following, the patient presented fever, tachycardia and capillary filling time  $>2$  sec, 28% bandemia and 39,700 leukocytosis in peripheral blood. Biopsy from the prior surgical procedure reported lymphadenitis with extensive caseous necrosis and small intestine compatible with acute peritonitis and subacute peritonitis with fibrinopurulent necrosis and chronic granulomatous



**Figure 4.** CT scan with contrast agent for head, thorax and abdomen with coronal and axial views reveals diffuse inflammation at neck with necrotic areas.

inflammation. Infectology Service added voriconazole due to dysthermia, respiratory pattern alterations and pathological findings.

Between the 26<sup>th</sup> and 49<sup>th</sup> hospitalization day, the patient continued with a poor evolution; finally, he presented cardiorespiratory arrest without responding to resuscitation maneuvers.

## CLINICAL CASE

Dr. María Guadalupe Labra Zamora (Pediatric Infectology, Resident)

Syndromatic diagnosis:

1. Diarrheic syndrome as per evacuations with reduced consistency as well as increased frequency
2. Infectious syndrome with abdominal focus as per fever, tachycardia, leukocytosis, bandemia and thrombocytopenia, metabolic acidosis and necessity to manage blood volume to retain normal arterial tension
3. Intestinal occlusion syndrome as per abdominal pain, distension, reduced peristalsis and vomit containing biliary fluids
4. Anemic syndrome as per pallor, tachycardia and 9.9 mg/dL hemoglobin; mean corpuscular volume was not evaluated so anemia could not be classified
5. Systemic inflammatory response syndrome with 39°C fever, leukocytosis with >10% immature forms and tachycardia

6. Respiratory insufficiency syndrome as per tachypnea and the need for mechanical ventilation

The aforementioned syndromes help us integrate the following nosological diagnoses:

- Septic shock with abdominal focus (considering the history of intestinal occlusion syndrome, which required surgical treatment twice) from an infectious syndrome with systemic inflammatory response, hypotension, hyperlactatemia metabolic acidosis and the use of crystalloid and amine solutions.
- Intestinal ischemia because of intestinal occlusion syndrome associated with leukocytosis, with or without thrombocytopenia and metabolic acidosis<sup>1</sup>
- Disseminated intravascular coagulation because of longer coagulation times, thrombocytopenia and hypofibrinogenemia; D-dimer was not quantified.
- Fungemia based on isolated yeasts from central hemocultures—according to clinical summary, report was produced 48 h after admission so peripheral blood culture must be from samples taken during placement of central catheter. This is very important to define whether it is a catheter-related colonization or an infection associated with central venous access according with IDSA (Infectious Diseases Society of America) 2009 guidelines.<sup>2</sup> Fungal infections are more frequent in immunocompromised patients and this patient presented added risk factors such as management with broad spectrum antibiotics, venous accesses and abdominal surgeries, among others. The pathogen most commonly identified in fungemias is *C. albicans*, which produces 70% of cases, followed by *C. glabrata* (10% of cases) and other non-*albicans* species.<sup>3</sup>
- Primary cellular immunodeficiency vs. innate immunodeficiency based on early age onset, male gender prevalence, granulomatous lesions found during lymph node biopsy, persistent lymphopenia, fungemia and torpid infectious evolution despite broad spectrum antibiotic and antifungal therapy as well as intensive hemodynamic management.

The aforementioned data together with abdominal data compatible with intestinal occlusion and fistula lead the diagnosis towards chronic granulomatous disease (CGD) according to the study by Marciano et al.<sup>4</sup>

The patient had three admissions: the first was at our institution where he was seen because of fever and irritability, abdominal syndrome, pain and NSAID management with nonsteroidal antiinflammatory drugs (NSAIDs), dehydration, metabolic acidosis and leukocytosis (which indicates a somewhat severe condition); however, he was discharged after 72 h.

There have been several studies since 1985 on the evaluation of infants  $<3$  months old who present fever and leukocytosis. Baraff et al. carried out a meta-analysis and found that even though a comprehensive clinical history is recorded and an appropriate physical examination is carried out, no evident infectious focus was located; however, up to 10% of these children may be experiencing a severe bacterial infection or a bacteremia diagnosed at a later stage. Laboratory tests should be carried out on these patients because they present a relative risk five times higher with leukocyte count  $>15,000/\text{mm}^3$ .<sup>5</sup>

According to clinical summary data, when the surgical problem was ruled out, the patient was discharged after 72 h; however, he presented severity data and it is not unusual for him to be admitted to another hospital within the next 24 h. He was managed there with exploratory laparotomy and ileostomy (without specifying if intestinal resection was performed). Histopathological tests were carried out on a mesenteric node, reporting granulomatous inflammation and was regarded as serous tuberculosis. The patient was managed accordingly.

We should remember that not every granulomatous lesion is a mycobacterial infection. There are other infectious and noninfectious entities that may also produce these lesions:

### **Infectious**

a) Tuberculous lymphadenitis is the prototype of granulomatous diseases; however, this is not the only option to be considered. Even though Mexico is regarded as endemic for tuberculosis and this entity is a public health problem, there were no data supporting such diagnosis for this patient. There were no epidemiological antecedents (positive Coombs) or bovine milk intake; these are important factors if we consider intestinal tuberculosis. We should remember that diagnosis is based on mycobacteria cultures or on a histopathological report that reports granulomas with caseous necrosis and the presence of acid/alcohol-

resistant bacillus (AARB). For intestinal tuberculosis, the etiological agent would be *M. bovis*, which is different from pulmonary tuberculosis. Treatment should have been different from what was administered.<sup>6</sup> We should also consider infections disseminated by BCG vaccine in patients with CGD or severe combined immunodeficiency disease (SCID) because the patient received such vaccination at birth; however, no mycobacteria were identified.

### **Non-infectious**

- a) Crohn's disease is another diagnostic possibility suggested by intestinal occlusion, abdominal pain, evacuations with reduced consistency and complications such as stenoses or fistulae. Although onset may occur at any age, maximum peak occurs between the second and third decades of life and is observed very rarely during the first months of life. This is a chronic disease and therefore was ruled out from this case. However, it is very important to mention this possibility because some studies report up to 11% of patients diagnosed with CGD were initially diagnosed with Crohn's disease.<sup>7</sup>
- b) Immunodeficiency, considering clinical profile and lymphopenia. Causes of lymphopenia include 1) HIV-AIDS infection, no parental history was reported for the patient's parents that lead us to consider this possibility; however, because of the patient's age and critical stage we ruled out this possibility, performing an HIV-ELISA test on the mother that resulted negative, 2) reduced production or survival of lymphocytes from primary immunodeficiencies. The pediatrician should suspect this possibility when a patient presents frequent, relapsing and severe infections as well as characteristics from involved microorganisms (opportunistic or with low virulence) because they can lead towards a possible immunity susceptibility.<sup>8</sup>
- c) Other associated factors include parental smoking status, stunted development and weight loss. The need for surgical intervention indicates the severity of associated infection.<sup>4</sup>

CGD was described by Berendes in 1957 as a lethal childhood granulomatosis. This is an inherited autosomal recessive disease in 11% of cases and presents an X-linked inheritance pattern in 89% of cases, having a higher

prevalence in males.<sup>4</sup> It is characterized by defective phagocytosis. Approximately 65% of patients present a mutation on *gp91phox* gene (oxidase of phagocytes) linked to chromosome X; 30% of autosomal recessive defects on *p47phox* gene and <5% on *p67phox* and *p22phox*.<sup>9</sup> These genes code for NAPDH enzyme subunits, which is essential to transport electrons and produce superoxide anions and several intermediary oxygen radicals (hydrogen peroxide and hypochloric acid) in phagocytic vacuole, allowing intracellular annihilation of microorganisms.<sup>10</sup> Alterations of this enzyme tend to favor fungal and bacterial infections; the first are more prevalent and more closely associated with morbimortality (especially aspergillosis).<sup>11,12</sup>

Age at onset is <2 years. Of cases, 65% present gastrointestinal compromise and develop chronic inflammatory granulomas. Symptomatic disease may include colitis/enteritis or gastrointestinal occlusion symptoms or occlusion of urinary tract by granuloma such as in the case of the patient presented here. A study with 140 CGD patients revealed that 32% of patients presented gastrointestinal compromise. Of these patients, 89% were linked to chromosome X and presented an unfavorable evolution.<sup>8</sup>

Granuloma development is a response to active infection but in many cases may be associated with an inadequate inflammatory response or a deficient degradation of inflammatory mediators and detritus such as absence of a respiratory burst in phagocytic cells. Production of oxidative agents is an important trigger for neutrophil apoptosis at inflammation sites, which is used during inflammatory response. Generally these patients suffer from severe infections at early ages caused by rare microorganisms (*Pseudomonas aeruginosa*, *Burkholderia cepacia*, *S. aureus* and *Serratia marcescens*, among others) that usually are catalase positive, which increases mortality.<sup>4,13</sup>

Another alteration these patients present (and that was described in the clinical case history in our patient) is defective scarring with surgical wound dehiscence. Therefore, this patient required a second exploratory laparotomy. Other data suggesting this diagnosis are alterations in complete blood count test such as anemia (up to 15% of cases), thrombocytopenia (20% of cases) and hypoalbuminemia (32% of cases), which were compatible with our patient's clinical history.

We should highlight that even though the patient was managed with antibiotic and antifungal therapies, he

presented a progressive condition and we observed no improvement. This has also been described in the international literature and it has been reported that even though an appropriate empirical antibiotic therapy is initiated, the intestinal inflammatory process does not experience changes.

Specific enteric infections such as salmonellosis, shigellosis or amebic dysentery occasionally present at the beginning and seem to be unrelated to CGD. Considering this patient had a long hospitalization, underwent invasive procedures and was managed with broad spectrum antibiotic therapy plus surgical wound dehiscence and perforation, antibiotic therapy should have been modified by December 18, focused on an abdominal infection.

Finally, the patient presented pneumonia, respiratory insufficiency, hemodynamic alteration and cardiorespiratory arrest without responding to advanced resuscitation maneuvers.

A precise immunodeficiency diagnosis requires advanced laboratory tests; however, suspicion needs two essential elements: consider immunodeficiency and a complete and guided clinical history. We should emphasize that this patient did not receive a screening test (aimed to confirm a defect of oxygen intermediate radical production); this test is carried out typically to diagnose CGD with nitroblue tetrazolium (NBT) tests<sup>14</sup> available at our hospital. These tests would have allowed diagnostic confirmation and initiation of a therapy that may have modified the outcome.

Integral approach of this case is not complete because a genetic assessment should be carried out to identify the type of inheritance and the probability that this disease presents again with a new pregnancy, especially considering the young age of this couple.

**Dr. Veronica Fabiola Moran (Head of Genetics Department)**

Because this male patient presented early and severe manifestations without family antecedents, he most likely suffered from CGD associated with chromosome X. However, it would be ideal to identify this defect at a molecular level to confirm the type of inheritance.

**Dr. Eduardo Bracho Blanchet (Head of General Surgery)**

Experience with other patients affected by this disease at our institution resembles this case: they present infectious

enteritis, ischemia, necrosis and intestinal perforation. If diagnosis had been carried out when the patient was alive, it would have been possible to apply systemic steroid therapy as described in the literature. Ostomy dehiscence also supports CGD diagnosis.

**Dr. Alejandra Nava Ruiz (Infectology Department)**

These patients present high mortality rates. Prophylaxis of 5 mg/kg/day itraconazole is indicated to prevent micotic agents plus the use of trimethoprim/sulfamethoxazole to prevent catalase-positive bacteria, which typically affect them. However, routine administration of interferon gamma (Imukin®) is a factor that modifies survival.

**Dr. Ma de Lourdes Cabrera Munoz (Head of Clinical and Experimental Pathology)**

We received sections from lymph node and small intestine carried out in the other institution and we observed chronic granulomatous necrotic inflammation on lymph node and connective tissue, and chronic as well as acute peritonitis. Special stains were negative for AARB, fungi or bacteria (Figure 5).

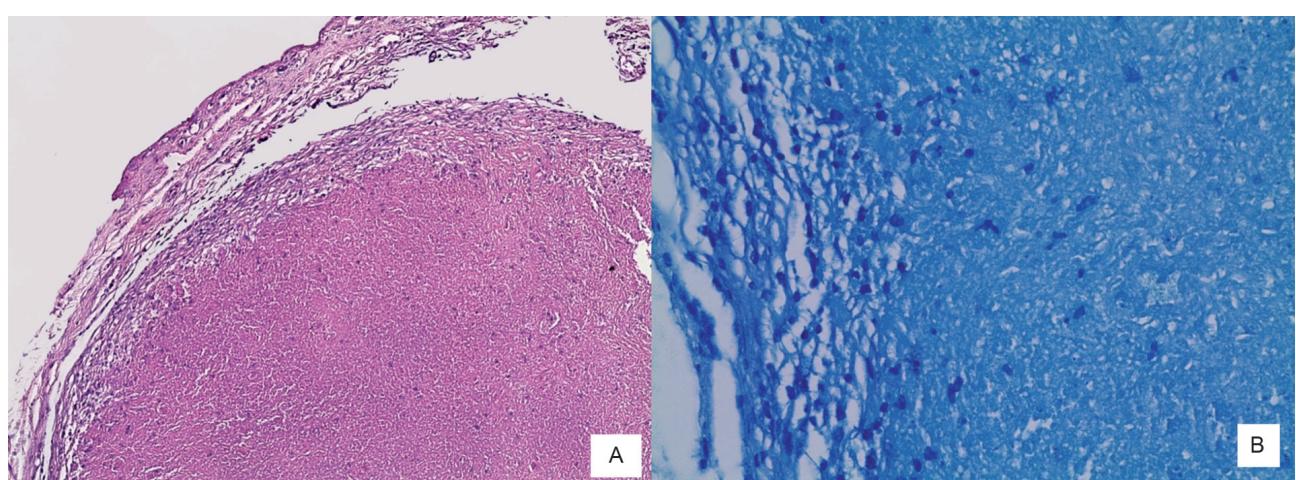
Resected segment from small intestine revealed intrawall inflammation with chronic granulomatous inflammation and acute and chronic peritonitis. Lymph node showed caseous necrosis. No microorganisms were identified (Figure 6).

Autopsy of a thin male child was carried out who presented gastrostomy and permeable ileostomy stomas,

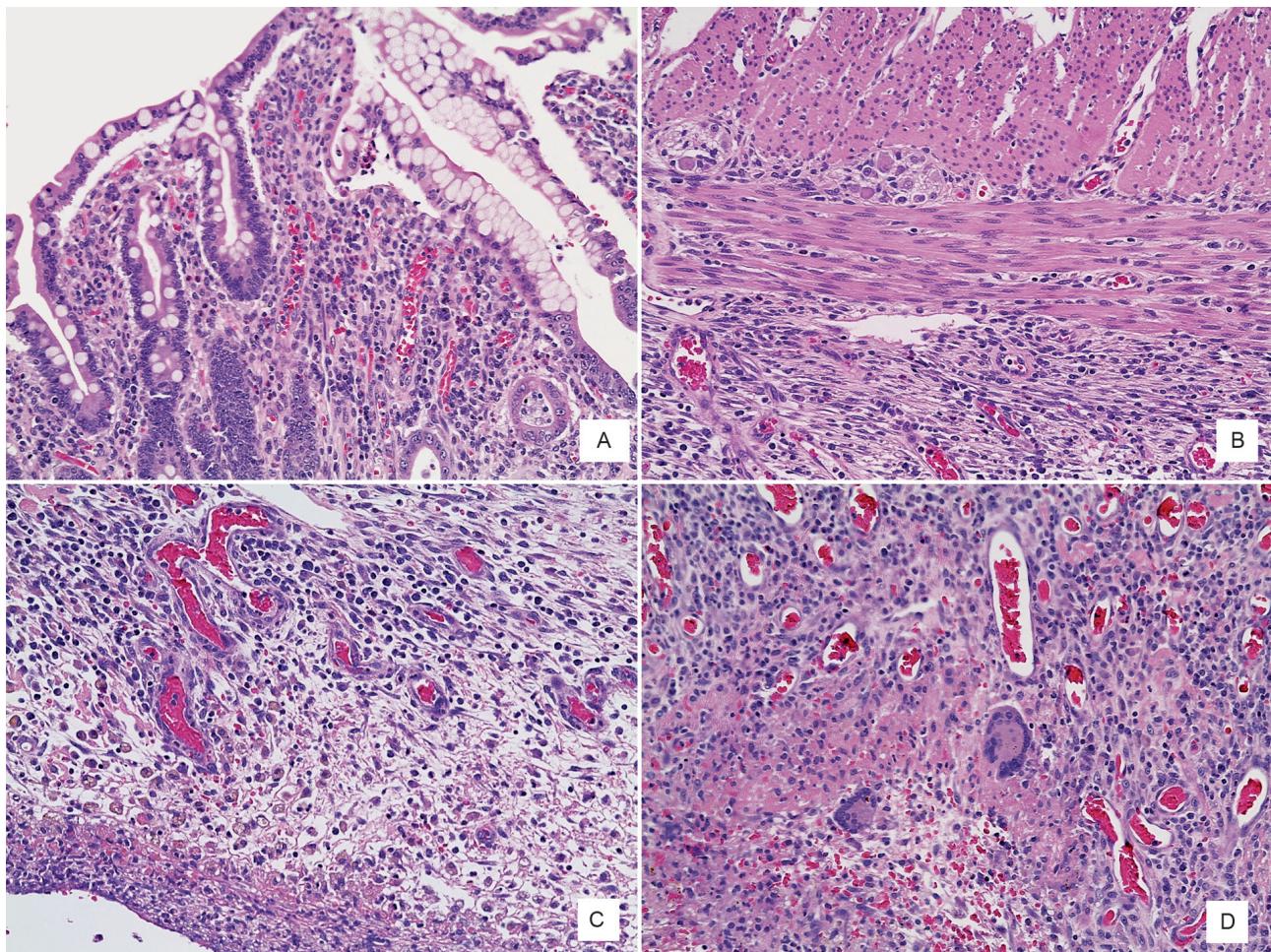
recently sutured abdominal surgical scar and irregularly bordered ulcer in occipital scalp region. Peritoneal cavity presented hepatocolic adhesions and peritoneum was dull with multiple yellow nodes extending to omentum and mesentery. Lungs showed multiple yellowish nodules up to 1 cm in diameter. Trachea and main bronchi presented ulcerated mucosa and their lumen contained a granular material with necrotic aspect. Lungs presented extensive damage characterized by multiple nodular necrotic lesions alternating with solid areas and distended areas in alveoli, affecting 80% of parenchyma (Figure 7). Several granulomas were histologically identified constructed by epithelioid macrophages, scarce lymphocytes and giant multinucleated cells, some of which were confluent and others with necrotic areas and microabscesses. We also observed areas of acute necrotic pneumonia (Figure 8). Stains were not compatible with AARB or fungi. In order to rule out tuberculosis, pulmonary tissue and mesenteric ganglion tissue from the second surgical intervention were sent for PCR testing for *Mycobacterium tuberculosis*, which was negative.

Liver was increased in size, weighing 750 g vs. 227 g expected, with a flat external surface and a congestive aspect. Cut surface was nodular and scarce yellowish dots were identified. Microscopically, there were scarce macrophages with yellow pigment and biliary pigment and hepatocytes with cholestasis and 15% macrovesicular steatosis in portal spaces.

Intestinal mucosa presented nonspecific chronic inflammation and pigmented macrophages at peritoneum.



**Figure 5.** (A) Lymph node with caseous necrosis. (B) Stain does not reveal acid-alcohol-resistant bacilli.



**Figure 6.** (A) Intestinal mucosa with nonspecific chronic inflammation. (B) Muscularis propria with lymphocyte infiltrate without compromise of myenteric plexus. (C) Several pigmented macrophages at peritoneum. (D) Granulomas with giant multinucleated cells due to foreign body in peritoneum.

Thymus presented intense decrease of lymphocytes at cortex and large macrophage groups with brownish-yellow pigment. Other findings were as follows: data compatible with kidney, intestine and bladder shock. Postmortem cultures were positive for *Pseudomonas aeruginosa* and *Enterococcus faecium*.

Presence of pigmented macrophages in different organs was first described by Dr. Benjamin Landing in 1957 in patients with relapsing infections syndrome. Subsequently, it was demonstrated that these patients presented CGD.<sup>15</sup>

Final diagnosis is established with enzymatic and molecular studies. In this patient, clinical evolution and histopathological findings strongly suggest CGD.<sup>16,17</sup>

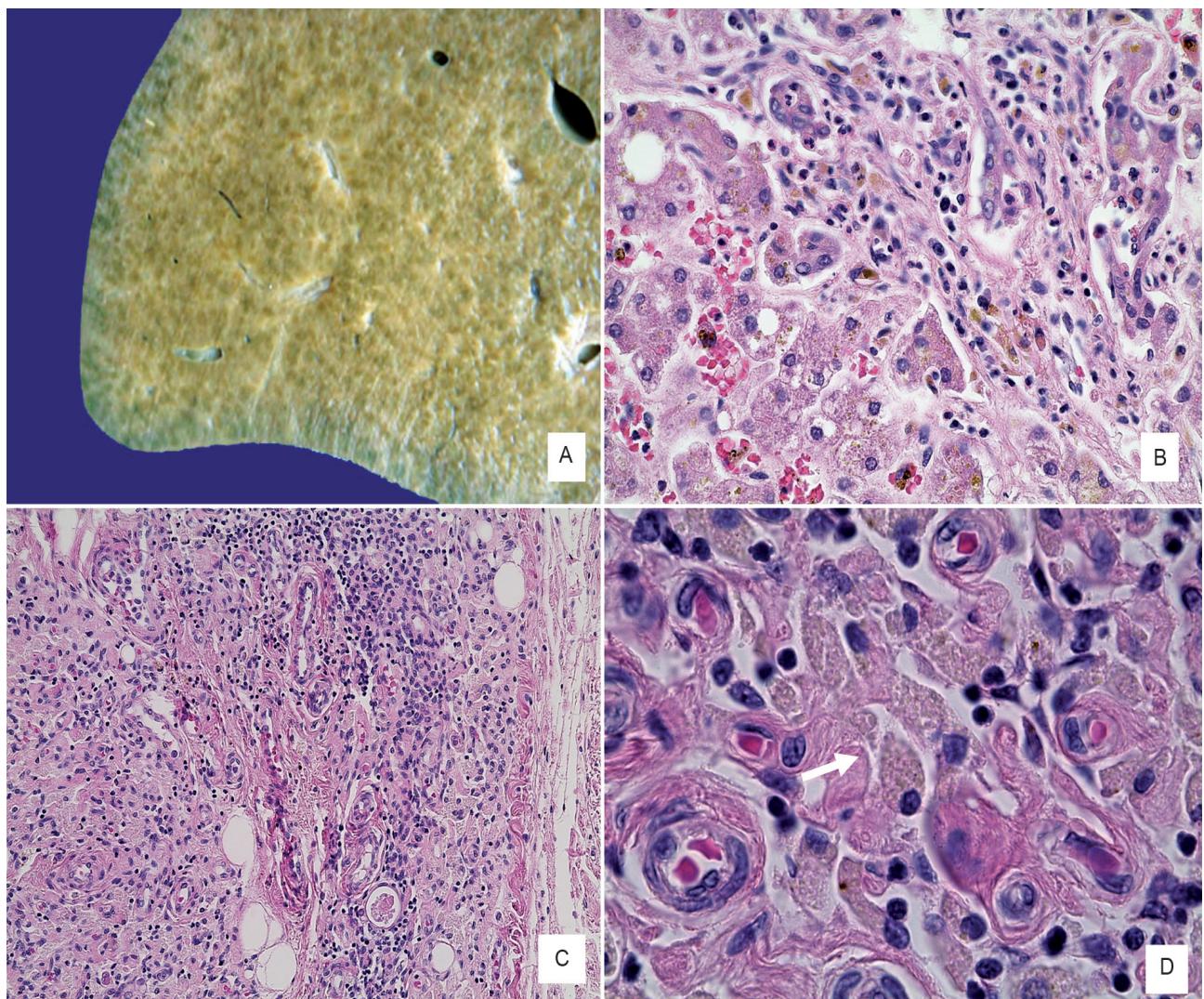
#### Final Anatomic Diagnoses

CGD affecting the following:

- Lymph nodes, lungs, liver, intestine, peritoneum and kidney
- Pigmented macrophages in thymus, lymph nodes and liver

Sepsis from *P. aeruginosa* and *E. faecium*

- Acute bilateral pneumonia
- Necrotic tracheobronchitis
- Acute purulent peritonitis
- Cholestasis and cholangiole proliferation



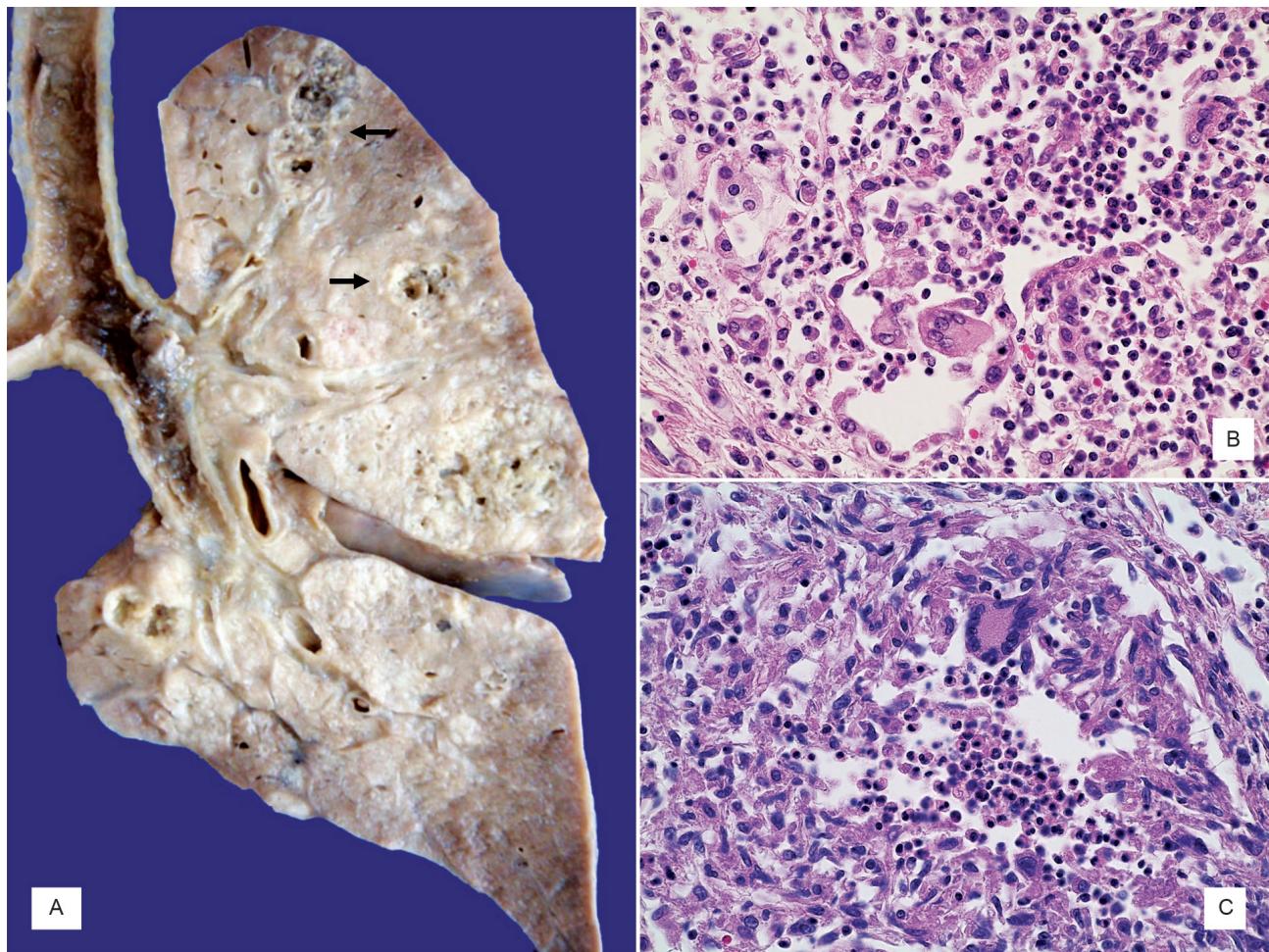
**Figure 7.** (A) Left lung with multiple confluent whitish-yellow cavitary lesions (arrows). Lumen at main bronchus and trachea is occupied by necrotic material. (B) Alveoli are occupied by polymorphonuclear cells and covered by smooth epithelium with scarce giant multinucleated cells. (C) Close-up of granuloma comprised of epithelioid cells, scarce lymphocytes and giant cells surrounding a microabscess.

Brain atrophy (600 g vs. 725 g expected)  
Thymus atrophy  
Left pneumothorax

#### Addendum

Patient's parents were contacted. They have an 8-month-old daughter who was tested with NBT and 123-DHR

flow cytometry. Results were compatible with CGD. This suggests inherited autosomal recessive disease. We confirmed that both parents did not have a consanguineous relationship, but because they belong to a small community, endogamy is likely to occur. At this time, the mother is 6-months pregnant.



**Figure 8.** (A) Liver with yellowish-green multinodular surface. (B) Macrophages with yellow pigment and biliary fluid at liver portal space. (C) Thymus microphotography with reduced lymphocytes and Hassall corpuscles. (D) Close-up of yellow-pigmented macrophages on thymus cortex (arrow).

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