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CLINICOPATHOLOGICALCASE

Congenital agranulocytocis

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INTRODUCTION

We present the case of a 7-year-old female with chronic neutropenia who was admitted due to rhinorrhea, fever and a skin lesion on the bridge of the nose. The patient's condition initially improved; however, fever persisted, with hemodynamic instability. The patient's death was due to septic shock from abdominal origin.

Imaging Findings
(Dr. Pedro Bazán Santos)

Coronal cut on computed tomography (CT) shows thickening of both maxillary antrum, ethmoid and sphenoid sinuses. There are no air fluid levels (Figure 1). However, coronal cuts of the abdomen show increased liver size, displacement of the intestinal loops towards the right side of the abdomen, mesentery displaced towards the left, and right iliac fossa with discrete swelling of the intestinal mucosa (Figure 2). On axial cuts, pulmonary fields are observed with ground-glass opacities and bronchovascular tissue is seen in its interior. There is no evidence of condensation or pneumothorax (Figure 3). Unfortunately, no x-rays were available at the time that the patient was diagnosed with neutropenic colitis.

1 Hematología
2 Cirugía General
3 Radiología e Imagenología
4 Infectología
5 Oncología
6 Patología

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CASE PRESENTATION

(Dr. Iván Rivas Rivera)

We discuss the case of a 7-year-old female patient referred to a second-level hospital at 3 months of age. Significant medical history reports that at 15 days of life the patient presented with anemia characterized by pallor and jaundice of the skin as well as hemoglobin count below the normal levels for age. The patient required transfusion of red blood cells. Diagnostic approach and the accompanying signs and symptoms are unknown.

At 3 months of age, the patient demonstrated a similar picture, for which she was referred to our hospital. On admission, a normocytic, normochromic aregenerative anemia was found, which causes a syndrome demonstrated by

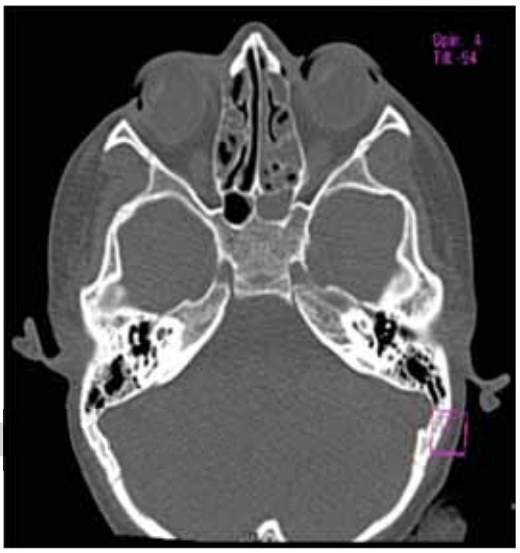

Figure 1. Computed tomography (CT) coronal cut in which thickening of the mucosa of maxillary, ethmoid and sphenoidal sinuses is observed. There are no air fluid levels.

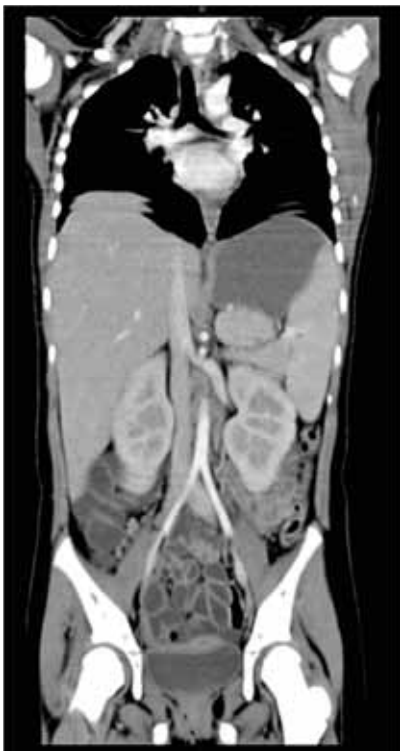

Figure 2. Coronal cuts of the abdomen show increased size in liver, displacement of the intestinal loops towards the right mid-abdomen, the mesentery displaced to the left, and the right iliac fossa with discrete thickening of the intestinal mucosa.

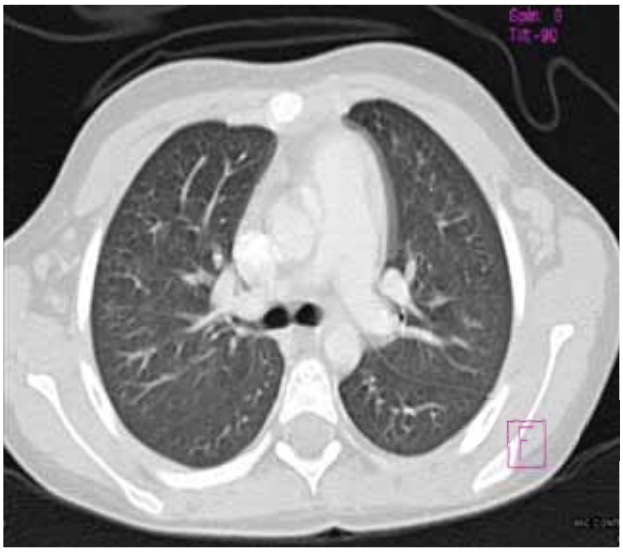

Figure 3. Axial cuts show pulmonary fields with ground glass appearance. In its interior is seen the bronchovascular portion. There is no evidence of condensation or pneumothorax.

skin pallor and hemoglobin levels outside the normal range. Once again, the patient required a transfusion of erythrocyte concentrate. She was evaluated by the hematology service, with the suspected diagnosis of Diamond-Blackfan anemia.

The diagnostic criteria for this disorder, as determined by international consensus, includes age <1 year, macrocytic anemia without other cytopenias, reticulocytopenia, bone marrow aspirate with decreased precursors of red blood cell line and neutrophil counts and normal platelets.[1] In our patient, CBC on admission reported 410 total neutrophils. There is no report in the clinical file of whether a bone marrow aspirate was done to determine the presence of precursor cell lines. Despite this, the patient was treated with steroids and her clinical condition improved. CBC results were within the normal range within 2 months of treatment initiation.

It is important to note that in the first bone marrow aspirate reported in the clinical summary, documentation was shown of the precursors of the three cellular series, even with hyperplasia of the red blood cell series and myeloid maturation up to bands, with neutropenia persisting on baseline blood count. These data contrast with the diagnosis of congenital bone marrow failure suggested during the patient's hospitalization, which leads us to consider a probable autoimmune etiology. In an attempt to study this disorder, anti-neutrophilic antibodies were requested, which were not carried out for an unknown reason.

Patient follow-up in the outpatient hematology was sporadic because the patient did not attend the scheduled appointments. Also, various laboratory tests were requested, which were also not performed. At 7 years of age the patient was admitted to the emergency room with a rhinosinusal syndrome based on the presence of hyaline rhinorrhea, later becoming yellow and with fever up to 38.5°C. Findings on physical examination demonstrated violaceous nasal mucosa, abundant purulent secretion, neck with lymphadenopathy of 2 cm located in the anterior cervical chain and a lesion on the nasal dorsum (0.5 cm in diameter) with a necrotic aspect and surrounding violaceous color.

During the initial examination, a diagnosis of systemic inflammatory response syndrome was made with septic shock and data of tachycardia, tachypnea, hypotension, delayed capillary refill and weak peripheral pulses, which warranted endotracheal intubation, detecting the rhinosinus process previously described as the apparent foci. Due to the presence of pancytopenia, alterations in coagulation time, hepatomegaly, generalized exanthema and hemo-

phagocytes in the bone marrow aspirate, diagnosis of secondary hemophagocyte syndrome was made.[2] A sample of the nasal lesion was taken and blastoconidias were found. Management for this was initiated and based on amphotericin B as well as third-generation cephalosporins and an aminoglycoside as part of the treatment for septic shock.

Due to the findings on imaging and laboratory studies and to the clinical picture, a diagnosis of fungal pansinusitis was made, as expected in a patient with long-standing severe neutropenia admitted with data of septic shock.

For management, a central venous catheter was placed. During the patient's hospitalization she experienced catheter-related sepsis and persisted with data of a systemic inflammatory response added to a growth in the blood culture of gram-positive cocci, which was later identified as *S. epidermidis.*

Ideally, a differential quantitative culture should be made between the peripheral and central culture to determine if the device is the source of infection. However, because the resource was not available in this case, it was decided to remove the catheter and to initiate vancomycin-based therapy.

It should be noted that patients with serious blood disorders require placement of central vascular access and improper care of these devices can lead to serious life-threatening complications.

It is necessary to carry out all aseptic and antiseptic measures to prevent colonization of the devices, thus providing quality care.

Due to the poor progress of the patient with persistent fever despite multiple antibiotic regimens, surgical drainage of sinuses was decided upon. A positive culture of the nasal mucosa was reported for *Candida albicans*. Based on this result, the patient received amphotericin B for 21 days.

As a complication of prolonged neutropenia, the patient presented data of neutropenic colitis supported by thickening of the colonic wall up to 9 mm and accompanied by abdominal pain, fever, vomiting and decreased stool consistency. Neutropenic colitis or typhlitis is a syndrome characterized by the classic triad of abdominal pain, fever and neutropenia. These data, as previously mentioned, were presented by the patient.

In patients with predisposing factors and diagnostic suspicion based on the clinical picture, it is necessary to request imaging studies for diagnostic confirmation. Currently, the best options are ultrasound (US) and computed tomography (CT), both tools that when bowel wall thickening >4 mm is detected, diagnostic suspicion is confirmed. There is controversy over which of the two imaging studies is better suited for measuring the intestinal wall. McCarville et al. described in 2005 that high definition US is the best option to measure the intestinal wall in pediatric patients.[3] The decision to perform US or CT should be based on the availability of the study and the experience and reliability of the radiologist who will perform the study.

The pathophysiology is not completely understood. It is believed that the cause is multifactorial, involving a compromise to the integrity of the colon wall, infection, bacteremia, necrosis, hemorrhage and perforation.[4] During the pediatric age, these characteristics are not exclusive to cancer patients. These may also occur in immunocompromised patients. In most cases they can be effectively managed with decompression, bowel rest, IV solutions and broad-spectrum antibiotics.

The initial use of empiric antibiotic is governed by the recommendations of treating the high-risk febrile, neutropenic patient: third-generation cephalosporin with pseudomonal coverage + vancomycin + metronidazole or monotherapy with carbapenem, adding an antifungal if severe fever and neutropenia continue >5 days.[5]

It is important to note that patients who persist with neutropenia for >7 days have a poor prognosis, with an increased incidence of complications secondary to neutropenic colitis. In our patient, a lesion was described suggestive of a perianal abscess, which further worsened the prognosis.

Surgical criteria in patients with diagnosis of neutropenic colitis were described in 1986 by Schamberg et al. and are still valid.[4] These include the presence of gastrointestinal bleeding despite correction of coagulopathy, thrombocytopenia and neutropenia, evidence of intraabdominal free air, shock refractory to intensive management and the presence of an intraabdominal process requiring surgical management in a neutropenic patient. On this basis, surgical management was ruled out during the first clinical picture of neutropenic colitis.

The patient continued with pancytopenia and respiratory and hemodynamic deterioration, again requiring endotracheal intubation. Subsequently, she presented data consistent with abdominal compartment syndrome, based on the 6-cm abdominal distension, ventilatory impairment manifested by the need for mechanical ventilation and shock data. With these data it was decided to place a rigid, intraabdominal catheter. Early diagnosis of this syndrome

allows for the application of a series of nonsurgical measures that have demonstrated an increase in the survival rate. Patients who show elevated intraabdominal pressure and organ dysfunction refractory to these nonsurgical measures have benefited from early decompression using placement of a rigid catheter. According to the review article on abdominal compartment syndrome by Carlotti and Carvalho in 2009, decompression through percutaneous catheter placement can avoid surgical resolution.[6]

The patient continued to demonstrate hemodynamic deterioration despite intensive treatment. It was necessary to perform exploratory laparotomy, finding abundant ascites, ischemic appendix and perforation in the sigmoid area. Total colectomy and ileostomy was done. Intraoperatively, the patient had two episodes of arrest with a duration of 22 and 3 min, respectively, which responded to the established management.

During laparotomy, necrotic or perforated intestinal segments should be resected. Performing ileostomy for only rendering the colon nonfunctional does not eliminate the source of septic shock. Despite surgical management with the use of vasoactive amines and blood transfusions, the patient persisted with hemodynamic instability along with data of persistent shock that finally led to cardiopulmonary arrest without response to advanced resuscitation maneuvers.

To summarize, this patient presented with prolonged neutropenia and septic shock secondary to fungal infection with poor evolution. She developed neutropenic colitis with abdominal compartment syndrome that required surgical treatment and continued with hemodynamic instability and, eventually, cardiac arrest.

Final diagnoses are as follows:

- Eutrophic female
- Probable autoimmune neutropenia
- Invasive fungal pansinusitis with *Candida albicans*
- Catheter-related sepsis due to *S. epidermidis*
- Neutropenic colitis
- Abdominal compartment syndrome
- Septic shock

Pathological Findings (Dr. Ma. Argelia Escobar Sánchez)

This patient had several previous biopsies and one cytology smear. The first biopsy received in the hospital is Q-2006-1528 in which trabecular bone fragments were observed without alterations and several intratrabecular spaces with ~90% cellularity. The three hematopoietic series are present. The myeloid series matured normally up to bands and segments. The erythroid series is limited and megakaryocytes show no alterations. There are no neoplastic cells or myelofibrosis (Figure 4). The second biopsy corresponds to Q-2007-732 and is very similar to the previous biopsy, with a cellularity of ~80-90% and the presence of the three series with normal maturation. There is maturation of the myeloid series and there are no neoplastic cells or myelofibrosis.

Subsequently, a new biopsy was received (Q-09-1608) demonstrating decreased cellularity of ~80%. The myeloid series continues to present maturation up to the bands and there is arrest in the maturation of the erythroid series. Clear cytoplasm demonstrates some macrophages and there are no neoplastic cells. Tissue was also received and identified turbinate mucosa and vestibule with tissue fragments covered by ulcerated respiratory epithelium, fibrosis and extensive inflammatory mononuclear infiltrate. No neutrophils and no fungi or other microorganisms were seen.

In 2009, another biopsy was received (Q-09-1775) corresponding to tissue identified as septum and turbinate mucosa with ischemic necrosis, thrombosis and chronic inflammation. There were no fungi or other microorganisms observed (Figure 5). A cytology smear was also received (C-09-347) corresponding to bronchial aspirate fluid without evidence of infection with *Pneumocystis jirovecci*. Finally, we received the results of the resection of the ileum, ileocecal valve, cecal appendix and colon, which showed extensive coagulative necrosis of the mucosa (Figure 6), with scant mononuclear inflammatory infiltrate, without evidence of neutrophilic infiltrate and numerous gram-positive and -negative bacterial colonies (Figure 7). There were no other microorganisms (Q-09-1950). Diagnoses of the biopsies and cytology are summarized as follows:

- Q-06-Q-1528 and 07-732—bone marrow with 90% cellularity and maturation of myeloid series. Negative for microorganisms and tumor cells.
- Q-09-1608—bone marrow with 80% cellularity. Turbinate mucosa and vestibule with chronic inflammation. Negative for fungi.
- Q-09-1775—septum and turbinate mucosa with ischemic necrosis, thrombosis and chronic inflammation. Negative for fungi.

- Q-09-1950—ileum, ileocecal valve, cecal appendix and colon. Neutropenic enterocolitis with gram-positive and -negative bacterial colonies.
- C-09-347—cytology of bronchial aspirate negative for *Pneumocystis jirovecci*.

The Department of Pathology later received the body of a female with normal facies. There was a fresh wound recently sutured with 20-cm long staples located in the mid-abdominal line and opening of the stomas. Bone marrow demonstrated decreased cellularity in relation to the previous biopsy of ~50% (Figure 8). The three series were decreased; however, maturation of myeloid series continued. There are also numerous plasma cells and macrophages of clear cytoplasm. Immunohistochemical staining was performed. Myeloperoxidase showed the presence of myeloid series and their maturation (Figure 9). CD138 staining showed the presence of an increased number of plasma cells.

The remainder of the organs of the mononuclear phagocytic system showed lymph nodes with significant decrease in cortical and paracortical lymphoid tissue and numerous macrophages located in the med-

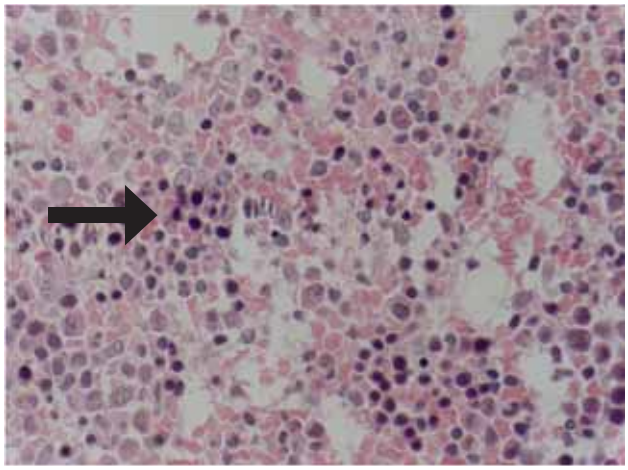

Figure 4. Bone marrow with 90% cellularity and maturation of the myeloid series (Q-06-1528) (H/E x40).

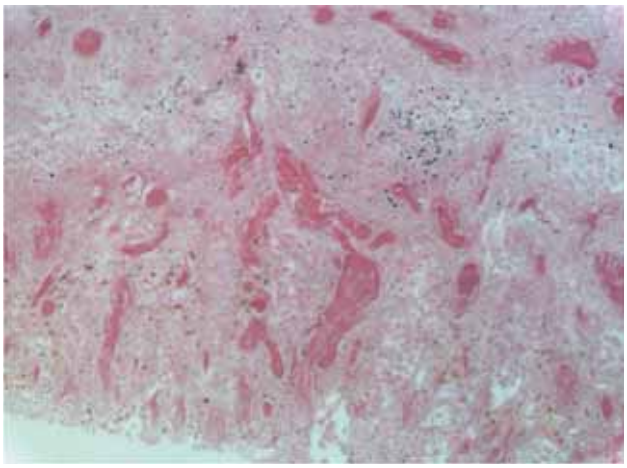

Figure 6. Wall of the colon with extensive ischemic necrosis and vascular thrombosis (Q-09-1950) (H/E x20).

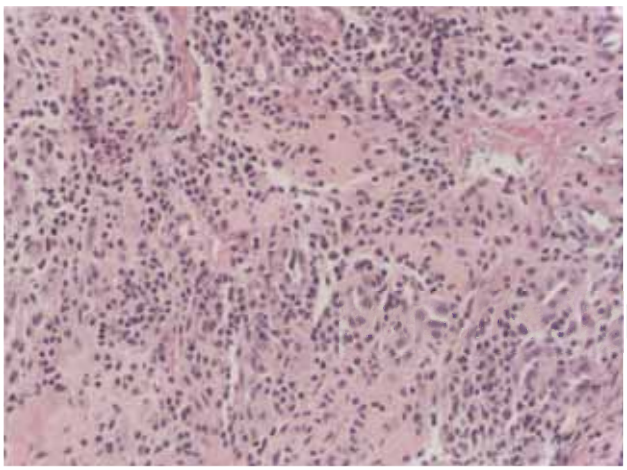

Figure 5. Septum and turbinate tissue with chronic inflammation, negative for fungus (Q-09-1775) (H/E x20).

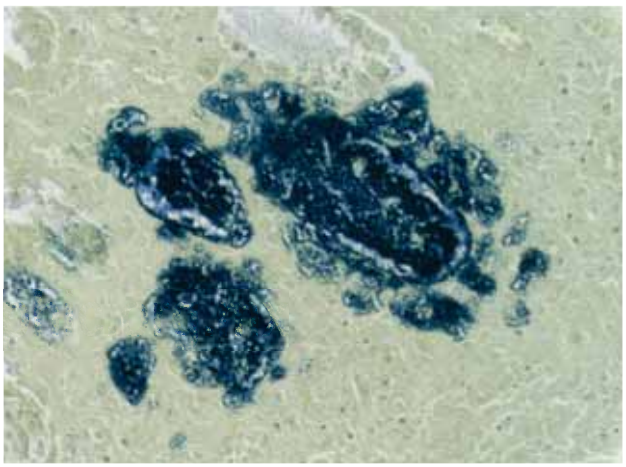

Figure 7. Intestinal wall with gram-positive colonies (Q-09-1950) (Gram x20).

ullary sinuses, some with clear cytoplasm and others with hemophagocytosis. The thymus showed decreased lymphoid tissue, fatty infiltration and calcification of Hassall's corpuscles.

The spleen was enlarged, weighing 174 g vs. an expected 66 g. Macroscopically, some areas showed congestion and microscopically there was decreased lymphoid tissue, congestion of the red pulp and hemophagocytosis. Immunohistochemical staining was performed with CD20 for B lymphocytes, which was positive in the germinal centers and the mantle zone, logically ruling out an alteration of the humoral immunity.

The liver was also increased in weight, 1500 g vs. an expected 680 g for age. There was congestion and histologically it was observed that the portal spaces showed no abnormalities. In the lobule, the sinusoids were dilated, congested and with hemosiderin deposition.

With these findings, it was determined that the primary disease was severe neutropenia because the bone marrow showed no alterations. The myeloid series was present with maturation, so it is suggested that the problem was peripheral, with destruction after its release. The causes may be secondary to autoimmune disease or infectious processes. In this case, due to the characteristics, a probable cause may be a congenital primary neutropenic autoimmune process with destruction of the neutrophils. However, the result of the antineutrophil antibodies was not taken into account; therefore, it can only be proposed.[7-10] Concomitant alterations are as follows:

- Reactive plasmacytosis
- Hemophagocytosis
- Sinus reactive hyperplasia in the mesenteric and peritracheal lymph nodes
- Congestive splenomegaly (174 g vs. 66 g)
- Congestive hepatomegaly (1500 g vs. 680 g)
- Thymic involution

This report described several cases of congenital neutropenia, which involve various molecular alterations that implicate several genes. There are various etiologies related to infectious processes, drugs and autoimmune causes, which is most likely in this case; however, the determination of antibodies such as GAT, GIFT, HNA antibody IgG-1 and HNA-2 is required.[7]

Among other findings, this piece corresponds to a fragment of colon showing mucosa with numerous small ulcers and extensive areas of necrosis and congestion. Small intestine demonstrated congestive and thin mucosa. Histological cuts show extensive ischemic necrosis of the mucosa, scarce mononuclear infiltrate extending to the serosa and numerous gram-positive and -negative bacterial colonies. No neutrophilic inflammatory infiltrate is seen.

The esophagus and stomach showed mucosal congestion and edema, histologically intact with congestion and contraction bands in the muscular wall. Pancreas, gallbladder and remainder of the small intestine were without alterations. With these findings, the following diagnoses were made:

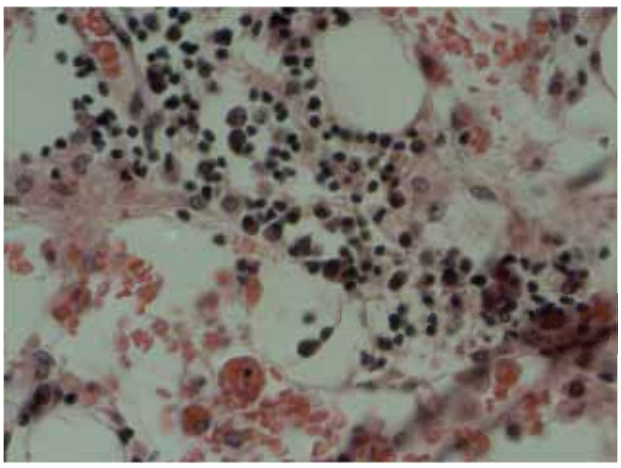

Figure 8. Postmortem hypocellular bone marrow with reactive plasmacytosis (H/E x40).

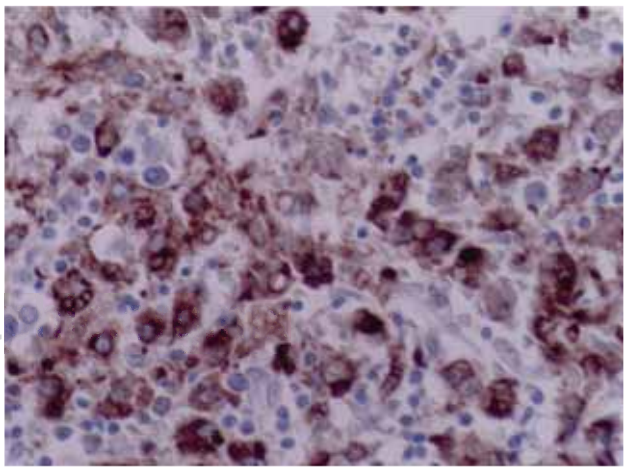

Figure 9. Myeloperoxidase showing the presence of myeloid series with maturation (x40).

- Necrotizing enterocolitis with numerous gram-positive and -negative bacterial colonies
- Acute peritonitis
- Status post-exploratory laparotomy and total colectomy (October 27, 2009)
- Status post-ileostomy (October 27, 2009)

The lungs weighed 650 g vs. an expected 253 g. Macroscopically, there were some areas of congestion and hemorrhage, predominantly in the left lung (Figure 10). Microscopically, there was hemorrhage and intra-alveolar edema (Figure 11). The heart weighed 175 g vs. an expected 100 g. It was noted to be structurally normal with areas of congestion in the adventitia of the great vessels. Different cuts showed data of hypoxia at the level of the cardiomyocytes. In the central nervous system, the brain had a weight within the expected weight of 1260 g vs. 1263 g; a normal convolution pattern with congestion of the subarachnoid vessels in the convexity as well as in the base, with left parietal occipital predominance. Microscopically, there was significant congestion of the subarachnoid vessels and data of neuronal hypoxia with retraction of the nucleus and hypereosinophilia of the cytoplasm of the neurons.

The kidneys had an increased weight of 380 g vs. expected 139 g. The corticomedullary relationship was preserved with marrow congestion and edema of the bladder mucosa. Histologically, there was glomerular capillary congestion and loss of tubular epithelium, i.e., acute tubular necrosis secondary to shock.

The endocrine system demonstrated congestion of parathyroid glands. The adrenal glands showed congestion. The ovaries showed primary and secondary dilated follicular cysts. The following anatomic data of shock were integrated:

- Hypoxic ischemic encephalopathy
- Acute tubular necrosis
- Acute alveolar damage
- Multivisceral congestion

With regard to the postmortem examination, blood culture, small intestine, colon and liver showed *Enterococcus faecium and Pseudomonas aeruginosa* (two morphological types). Left and right lung, spleen and cerebrospinal fluid were negative.

Hematology Comment
(Dr. Máshenka Moreno González)

With regard to the neutropenia presented by this patient, three differential diagnoses must be taken into consideration:

- Severe congenital neutropenia
- Autoimmune lymphoproliferative syndrome
- Autoimmune neutropenia

Severe congenital neutropenia is uncommon[11] and causes severe infections from the first month of life, without spontaneous remission of the neutropenia (as presented in this case after steroid treatment). In the bone marrow aspi-

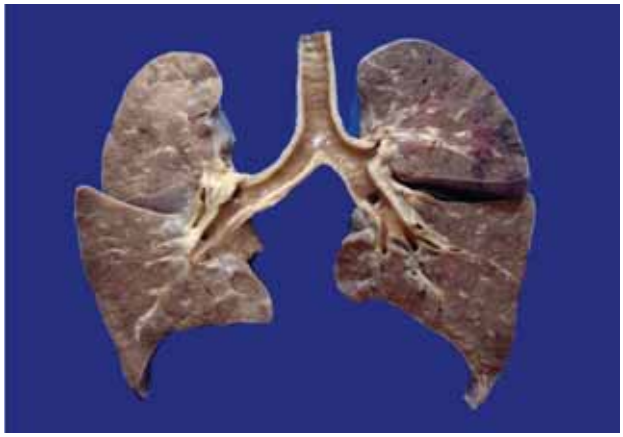

Figure 10. Sectional cut of lungs with hemorrhage and congestion, mainly on the left.

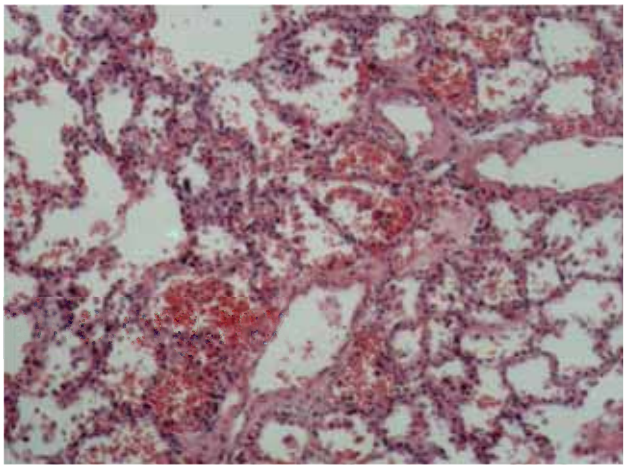

Figure 11. Histological cut of the lungs corroborating intraalveolar hemorrhage (H/E x20).

rate there is an arrest in the maturation of myeloid series in promyelocytes, criteria not presented by this patient.

The autoimmune lymphoproliferative syndrome can be suspected in the face of the results of the bone marrow that the patient did present, as it was a reactive marrow with hyperplasia of the three series as well as lymphadenopathies. However, the remaining studies were not available to confirm the diagnosis (such as laboratory tests to exclude autoimmune processes and, above all, flow cytometric quantification of double-negative T cells). Also, the pathology report of lymph nodes mentioned by Dr. Escobar was not compatible with this diagnosis, as follicular hyperplasia with paracortical expansion would be expected, and it was not found in this patient.[12-15]

Therefore, it is believed that the most probable diagnosis was autoimmune neutropenia because it is a more frequent and acquired cause. Neutropenia in this patient started from birth. It is notable that the patient responded to steroids, which were administered for the pure aplasia of the red blood cell series. However, as mentioned in the baseline blood count, recovery was also seen in the neutrophils. It has been shown that in some patients the trigger for autoimmune neutropenia is an infection due to parvovirus B19. During the first admission this patient presented pure aplasia of the red blood series, which may have been caused by parvovirus B19 and subsequently triggered the autoimmune neutropenia.[9,16]

Infectology Comment (Dr. Sarbelio Moreno Espinosa)

In this case, because the neutropenia was severe and chronic, a comment was made whether the patient would have benefited with the administration of prophylactic antibiotics to decrease the risk of infection; however, most experts agree in that there is no advantage in initiating prophylactic antibiotics than in treating the infection when it occurs.[17] As a preventive measure, good oral hygiene with brushing and careful massage is recommended, as well as regular dental visits.[18] The other point for discussion was that, at some time, it was decided to withdraw antibiotics because of their relationship with fever.

Fever is believed to be associated with antibiotics when there is a gradual or abrupt elevation in body temperature during antibiotic therapy, despite the lack of evidence of exacerbation of the infection. Even though the mechanism by which fever is induced by antibiotics is completely unknown, an immunological involvement is strongly suggested, i.e., an allergic reaction to the drug.[19]

This is a case of a patient with corroborated neutropenia, which justifies the presence of fever due to an infectious cause. Therefore, it does not meet the definition of fever associated with antibiotics. This was corroborated with remission of the fever at the time it was raised to a greater spectrum.

Through the use of clinical retrospective uncontrolled studies and two controlled clinical trials, the potential benefit of the combination of new antifungal agents in the treatment of systemic infections by filamentous fungi has been recently demonstrated. The combinations used were a polyene (such as amphotericin B) plus an echinocandin (such as caspofungin), amphotericin B with an azole (such as voriconazole) and voriconazole + caspofungin. In some cases, an antagonistic response has been confirmed between amphotericin B and voriconazole, but in other reports this situation has not been reported.[20] With regard to infections due to candida, there is a report of the successful combination of amphotericin B with caspofungin in infections due to *Candida glabrata*.[21]

Commentary of Transplantation of Hematopoietic Progenitor Cells (Dr. Felix Gaytan Morales)

Transplantation of hematopoietic stem cells is a method currently used to resolve a wide variety of malignant and nonmalignant problems. Most of the problems with indications for transplant arise from the time of diagnosis.

It is noteworthy that there are indeed pathologies in which, when there is a relapse after the start of treatment (such as normal risk leukemias) or in the case of diseases refractory to treatment (lymphomas, autoimmune diseases such as lupus erythematosus, HIV, congenital neutropenia), these are indications for hematopoietic stem cell transplantation.[22-27]

In the particular case of this patient and as related to the study protocol in our service, the first consult, or interconsultation if the patient is hospitalized, is to evaluate whether the patient meets the criteria for transplant

based on the biological, immunological and genetic characteristics of the disease, thereby initiating the study protocol. The decision should not be taken to transplant a patient if a diagnosis has not been established and if the patient is medically unstable. For this reason it is believed that the assessment to perform a transplant on this patient was done in a hurried manner, according to what has been previously explained.

Final Comment
(Dr. Io Daiela Castillo Martínez)

This patient presented various situations that must be taken into account. First of all, there is the importance of a timely and accurate diagnosis of neutropenia, studying multiple causes and taking into account different options, without focusing on only one pathological consideration. From this approach, directed treatment and patient prognosis will undoubtedly depend.

The neutropenic colitis presented by the patient should make us reflect on the clinical assessment—both medical and surgical—moment by moment. We should not overlook the indications for early radical surgery in order to achieve greater improvement in survival and prognosis of septic shock. Finally, the determination of whether a patient is a candidate for bone marrow transplantation should be done with proper diagnosis and optimal conditions, not when the patient is unstable.

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