Neutropenic fever of unknown origin and disseminated granulomatous disease in a patient with acute lymphoblastic leukemia

Fiebre de origen desconocido neutropénica y enfermedad granulomatosa diseminada en un paciente con leucemia linfoblástica aguda

Febre de origen desconhecida neutropênica e doença granulomatosa disseminada em um paciente com leucemia linfoblástica aguda

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Abstract:

An 18-year-old male was admitted for his second induction chemotherapy treatment for an acute lymphoblastic leukemia with cyclophosphamide, cytarabine, and mercaptopurine. Later, he presented with high fever, abdominal pain, non-bloody diarrhea, portal hypertension and leukopenia. Stool sample analysis, blood cultures and extensive work-up were negative. The only microbiologic evidence was the presence of cytomegalovirus DNA detected by PCR. A profound hypogammaglobulinemia was documented. Pathology material reported non-caseating granulomas in liver, bone marrow, duodenum and colon with negative cytomegalovirus immunostaining. What is your diagnosis?

Key words: *fever of unknown origin; neutropenia; granuloma*

Resumen:

Un varón de 18 años se internó para recibir el segundo ciclo de inducción por una leucemia linfoblástica aguda con ciclofosfamida, citarabina y mercaptopurina. Posteriormente, presentó fiebre alta, dolor abdominal, diarrea no sanguinolenta, hipertensión portal y leucopenia. El análisis de materia fecal, cultivos de sangre y una evaluación exhaustiva fueron negativas. La única prueba microbiológica fue la detección de ADN de citomegalovirus en sangre por PCR. También se documentó una hipogamaglobulinemia profunda. Se encontraron granulomas sin necrosis de caseificación en el hígado, médula ósea, duodeno y colon con inmunohistoquímica negativa para citomegalovirus. ¿Cuál es su diagnóstico?
Palabras claves: *fiebre de origen desconocido; neutropenia; granuloma*

Resumo

Um homem de 18 anos foi internado para o segundo ciclo de indução de leucemia linfoblástica aguda com ciclofosfamida, citarabina e mercaptopurina. Ele desenvolveu febre alta, dor abdominal, diarreia não sanguinolenta, hipertensão portal e leucopenia. A análise das fezes, as hemoculturas e uma avaliação abrangente foram negativas. A única evidência microbiológica foi a detecção de DNA de citomegalovírus no sangue por PCR. Hipogamaglobulinemia profunda também foi documentada. O material patológico relatou granulomas não caseosos no fígado, medula óssea, duodeno e cólon com imunohistoquímica negativa para citomegalovírus. Qual é o seu diagnóstico?

Palavras chaves: *febre de causa desconhecida; neutropenia; granuloma*

CASE PRESENTATION

An 18-year-old male recently diagnosed with T-cell acute lymphoblastic leukemia (ALL) was admitted for his second induction chemotherapy treatment with cyclophosphamide, cytarabine, and mercaptopurine. He had no other medical records. He lived with his family in the Buenos Aires suburbs and had 5 cats.

On the 25th day after chemotherapy was initiated, he presented with high fever (39 ºC) and chills, generalized abdominal pain and non-bloody diarrhea.

The patient had a palpable spleen, hepatomegaly and papillitis in the left eye. His BMI was 16 kg/m2. Brain and chest CT, and transesophageal echocardiogram were normal.

Blood analysis revealed hemoglobin 8.8 g/dl, neutrophils 240 x 10^3/µl, lymphocytes 490 x 10^3/µl, platelets 74 x 10^3/µl, total bilirubin 0.2 mg/dl, ALAT 72 UI/l, ASAT 26 UI/l, ALP 193 UI/l. Serum protein electrophoresis showed an increased alpha1-fraction (0.33 g/dl) and profound hypogammaglobulinemia (0.4 g/dl). IgA, IgG, and IgM were low (39, 665 and 7 mg/dl respectively).

A few weeks later, he progressively developed a mixed cholestatic-hepatotoxic pattern of liver function tests (total bilirubin: 3.9 mg/dl, direct bilirubin: 3.8 mg/dl, ALAT 938 IU/l, ASAT 885 IU/l, ALP 2,261 IU/l, GGT 331 UI/l). Prothrombin time was normal. Ultrasound reported hepatosplenomegaly, intact extrahepatic bile duct and no signs of thrombosis of the portal vein on Doppler exam. Serologic test results for hepatitis A, B and C were negative.

The patient underwent an exploratory laparoscopy because of sudden worsening of abdominal pain with peritoneal signs. The only finding was mild ascites (66 neutrophils/µl, serum-ascites albumin gradient of 1.6, negative culture). CT scan of the abdomen had reported signs of colitis and periportal oedema. A transjugular liver biopsy was obtained. Hepatic venous pressure gradient was 11 mmHg, compatible with portal hypertension.

The patient persisted with intermittent episodes of abdominal pain, distension, absence of bowel sounds and constipation alternating with diarrhea, along with daily fever, despite neutrophil recovery (1.96 x 10^3/µl), although leukopenia persisted (2.71 x 103/µl). Upper and lower gastrointestinal endoscopies were performed.

Pathology results **(Figure 1)** reported non-necrotizing granulomatous inflammation of duodenum and colon with negative cytomegalovirus (CMV) immunostaining, hypocellular bone marrow with 1 non-necrotizing granuloma with negative PAS and Ziehl Neelsen stains; also a few structures suggestive of CMV cytopathic effect were seen. The liver also showed non-necrotizing granulomatous inflammation.

Acid-fast bacillus staining and culture was negative in all tissue samples, including myeloculture, as was GeneXPert® test on the duodenal tissue. PCR tests for CMV, Histoplasma spp. and Bartonella spp. in biopsy materials were negative. Plasmatic CMV viral load was 3,168 copies/ml (viral load log10= 3,5). Serum antibodies for Brucella spp. using Huddleson, Bengal rose test, BPA, SAT, 2-mercaptoethanol agglutination test, complement fixation test, BrucellaGliyco-iELISA and RSAT were negative, as were serum IgG, IgM, and PCR for Bartonella spp.

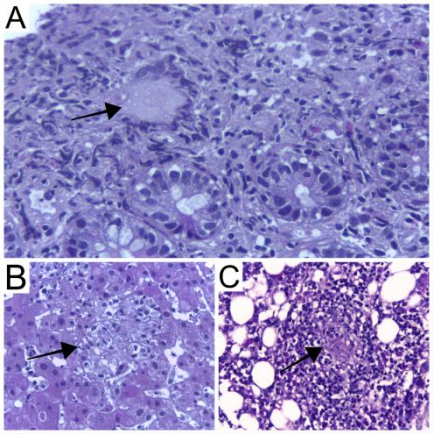

Figure 1: Nonnecrotizing granulomas with multinucleated giant cells (black arrows) in the duodenum (A - H&E stain, X400), liver (B - H&E stain, X400) and bone marrow (C – PAS stain, X400).

Cerebrospinal fluid analysis reported an opening pressure of 15 cmH2O, 2 cells/µl, 114 mg/dl of protein and an angiotensin-converting enzyme level < 1.5 U/l (normal < 2.5 U/l). PCR for CMV, Epstein Barr and herpes viruses I and II were negative.

Serum toxoplasmosis, herpes virus, Epstein Barr, herpes viruses I and II, Chagas disease, VDRL, ANA, PR3-ANCA and MPO-ANCA were negative.

In all, 10 sets of blood cultures obtained had no bacterial growth. Lysed-blood cultures, serial serum galactomannans, assay for C. difficile toxin detection, serial fecal sampling, and PCR-molecular detection of Strongyloides stercoralis in fecal sample were negative.

We initially treated this patient with broad-spectrum antimicrobials empirically. Ganciclovir was administered for 30 days, after which CMV viremia was negative. He also received amphotericin, doxycycline, and corticoids as premedication for blood transfusions. With these measures, the fever pattern became relapsing.

Our first diagnostic approach was an immune-deficient or neutropenic fever of unknown origin (FUO)[1], caused by a noncaseating granulomatous disease, responsible for portal hypertension, chronic diarrhea, pancytopenia and papillitis of the left eye.

This patient had several secondary immunodeficiencies: malnutrition, neutropenia, lymphopenia, weakened mucosal barriers caused by chemotherapy, disruption of epithelial and mucosal barriers by central lines and urinary catheters, corticoid use, CMV infection and hypogammaglobulinemia. 65 % of adolescents and young adults with ALL were found to present with hypogammaglobulinemia and an increased frequency of febrile neutropenia episodes and infections, compared with patients with normal IgG levels[2].

Granulomas are organized collections of activated macrophages or histiocytes as the result of a chronic inflammatory process to an antigen or autoantigen that is persistent or difficult to remove[3]. Hypogammaglobulinemia, as in common variable immunodeficiency, may be a cause of granulomas[4].

Infections are the commonest causes of disseminated granulomatous disease; in fact, some experts regard an infection as the root cause of all such disorders but that it remains undetected in some[5]. A retrospective review of 308 biopsies with non-necrotizing granulomas confirmed sarcoidosis as the leading cause (56 %)[6]. Two plausible endemic infectious etiologies in Argentina were unsuccessfully pursued: 1) Tuberculosis, which may also present with non-necrotizing granulomas in immunocompromised patients[7], and 2) Histoplasmosis. The combination of FUO, granulomatous disease, eye involvement and past contact with cats oriented us towards Bartonella spp.infection[8]. The most characteristic and common ocular finding of systemic bartonellosis is neuroretinitis (optic disc oedema with macular star)[9], and no evidence of such infectious agent was found. Brucellosis was also ruled out.

We decided to empirically initiate a second-line treatment for tuberculosis, since liver function test was abnormal (ethambutol, levofloxacin, amikacin and meropenem).

Fever defervesced after 5 days, his abdominal manifestations progressively disappeared, leukopenia and neutropenia resolved in a few weeks, and liver function tests eventually normalized. The patient successfully completed the second induction chemotherapy a month after the anti-tubercular drugs were started, and he is currently receiving the maintenance therapy at home. He is a month away from completing a full year of tuberculosis treatment.

The patient was admitted 4 months later for herpes zoster in the left inferior limb. He had been afebrile and without diarrhea.

WHAT IS YOUR PRESUMPTIVE DIAGNOSIS?

Unfortunately, we were not able to reach a definitive diagnosis despite a thorough medical history and physical exam, an extensive work-up and numerous efforts. It remains unanswered to us whether this unidentified etiology was successfully treated, or whether it was a self-limiting one, either infectious or non-infectious (for example, sarcoidosis[10]). The fact that all manifestations arose during neutropenia, combined with the profound involvement he exhibited while febrile, strongly suggested an infectious etiology. On the other hand, given our local epidemiology, and the temporal coincidence between the initiation of the antitubercular medications and the

patient's clinical improvement, an incomplete form of tuberculosis remains as the most likely diagnosis to us, even though we were not able to reliably prove it.
The most frequent causes of noncaseating granulomas are presented in **Table 1**.

TABLE 1
Etiologies of noncaseating granulomas

A. INFECTIOUS	B. NONINFECTIOUS
Mycobacteria	Berylliosis
Atypical mycobacteria	Carcinomatosis
Tuberculosis (*)	Drug reaction
Leprosy	Eosinophylic granuloma
Bacteria	Foreign body reaction
Bartonella henselae infection	Granulomatous arteritis
Brucellosis	Hypogammaglobulinemia
Lysteriosis	Hystiocytosis X
Melioidosis	Lymphomas
Nocardiosis	Sarcoidosis
Q-fever (Coxiella brunetti)	Ultrafiltration
Spirochetes	Wegener's granulomatosis
Syphylis	
Yaws (T. pallidum subspecies pertenue)	
Fungi	
Blastomycosis	
Candidiasis	
Coccidioidomycosis	
Criptococcosis	
Histoplasmosis	
Mycetoma	
Sporothrix schenckii	
Protozoa	
Leishmaniasis	
Virus	
Cytomegalovirus	
Infectious mononucleosis	
Measles, mumps	
Actinomyces	
Whipple's diesaease	

Most frequent etiologies of noncaseating granulomas.
Modified from Zumla[11] and James[12].
* In immunocompromised patients [7]

Limitaciones de responsabilidad
La responsabilidad del trabajo es sólo de los autores

Conflictos de interés
Ninguno

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Originalidad del trabajo
Este artículo es original y no ha sido enviado para su publicación a otro medio de difusión científica en forma completa ni parcialmente.

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Participación de los autores
Quienes participaron en la concepción del diseño, recolección de la información y elaboración del manuscrito, son públicamente responsables de su contenido y aprobando su versión final.

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