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LETTER TO EDITOR

Disseminated Tuberculosis in a Patient with Autosomal Recessive p47^{phox} Chronic Granulomatous Disease

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To the editor,

Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI) affecting the function of phagocytes [1]. The CGD is caused by pathogenic variants in any of the genes encoding for the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits, leading to a null or impaired production of reactive oxygen species (ROS) in all phagocytic cells [1]. Hemizygous pathogenic variants in the *CYBB* gene, encoding for the gp91^{phox} protein, result in the X-linked recessive (XR) form of CGD, which is the most common genetic cause of CGD in America and Europe [2]. Autosomal recessive (AR) CGD results from by biallelic pathogenic variants in the *CYBA*, *NCF1*, *NCF2*, *NCF4*, and *CYBC1* genes, which encode for the p22^{phox}, p47^{phox}, p67^{phox}, p40^{phox}, and Eros proteins, respectively [1]. AR cases are more prevalent in certain regions with high degrees of consanguineous marriages [3]. Clinically, CGD patients present with dysregulated inflammation and diversity of recurrent bacterial including mycobacteria, and fungal infections, requiring a high index of suspicion for its diagnosis [1, 2]. We report an adult patient previously diagnosed with CGD due to *NCF1* pathogenic variation who developed severe abdominal and pulmonary tuberculosis (TB) [1].

A 28-year-old female was born from consanguineous parents in a rural area in the central-north of Mexico. She received the BCG vaccine at birth with no adverse reaction noted. She had a history of multiple pneumonia and lymphadenitis episodes during childhood and was diagnosed at 11 years old with AR CGD due to the most frequent biallelic deletion, c.75_76del/75_76del, in *NCF1* [1]. After diagnosis, she received itraconazole and TMP-SMX as prophylactic treatment with irregular compliance. Her younger sister was also diagnosed with CGD at the age of 10 years old; she also received the BCG vaccine at birth without adverse reaction. She arrived at the emergency department with diffuse abdominal pain and distention of 2 weeks of evolution. On physical examination, she had tachycardia, hypotension, fever, ascites, and peritoneal irritation signs. Laboratory findings revealed microcytic anemia (Hb 8.4 gr/dL [13–17.5], MCV 77 fL [80–95]), lymphopenia (220/mm^3 [4500–11,000]), and elevated C-reactive protein (32.6 mg/dL [< 0.3]). Thoraco-abdominal CT scan showed right lung apical micronodules (Fig. 1A), bilateral pleural effusion, and intra-abdominal free fluid accompanied with free pericecal air spots suggesting distal ileal perforation (Fig. 1B). A laparotomy showed multiple millimetric nodules on the peritoneal cavity and omental thickening (Fig. 1C), draining 1.7 L of clear intraperitoneal fluid. Left

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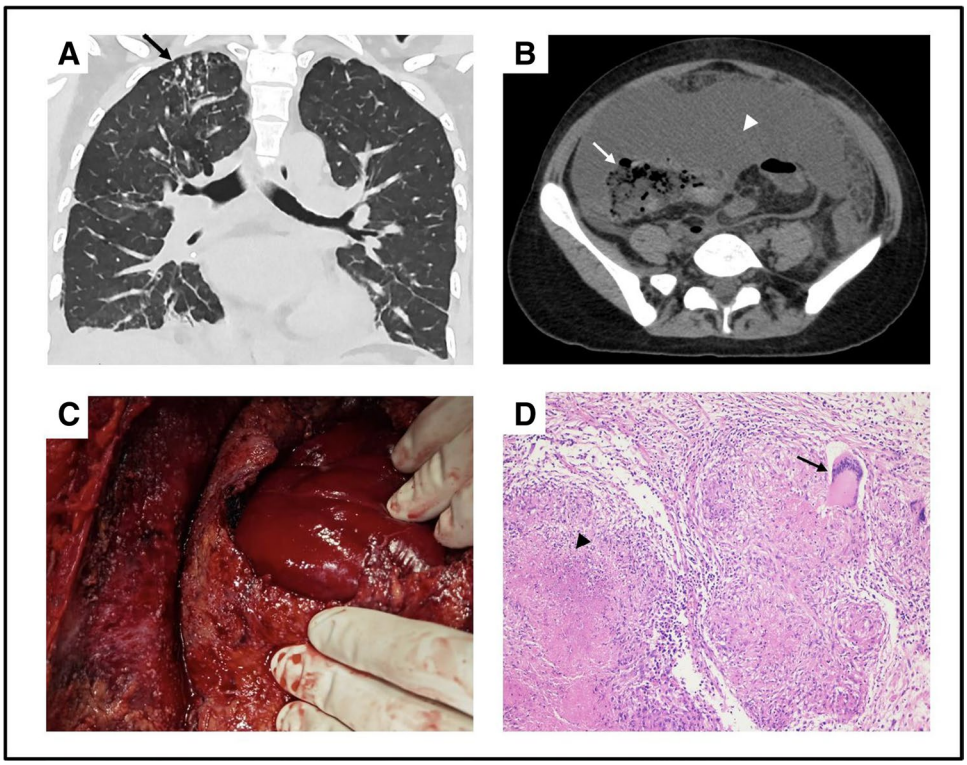

Fig. 1 Tuberculosis and chronic granulomatous disease. **A** Computed tomography (CT) of the thorax showing right apical micronodules (arrow). **B** Abdominal CT showing intraperitoneal free fluid (arrowhead) with accompanying pericecal air-spots (arrow). **C** Abdominal cavity with multiple nodules on peritoneum and thickened omentum. **D** Histological section of the peritoneum stained with hematoxylin and eosin (×40) in which granulomas, caseous necrosis (arrowhead), and Langhans giant cells (arrow) are identified

oophorectomy and appendicectomy were necessary due to marked peri-appendiceal inflammation with adhesions and enlarged left ovary with hemorrhage. The patient did not have an abdominal perforation. Histopathological specimens of the ovary, omentum, peritoneum, cecum, and appendix reported granulomas with central caseation necrosis and giant multinucleated cells (Fig. 1D). Staining for bacteria and fungi such as Ziehl–Neelsen was negative; the Xpert MTB/RIF assay® in the peritoneal fluid was also negative. Despite the negative laboratory results for mycobacterial infection but in agreement with the relationship between CGD and TB in developing countries [1], first-line oral anti-TB agents were initiated. On postoperative day 8, traces of intestinal fluid were observed over the surgical incision; the contrast-enhanced CT scan showed a fluid collection around the cecum stump with accompanying oral contrast filling. A laparotomy revealed appendiceal stump leakage repaired with primary closure. During postoperative recovery, the patient presented acute respiratory failure due to pulmonary artery embolism requiring mechanical ventilation and full-dose anticoagulation. On postoperative day 10, the patient presented fever and peritoneal irritation; a third laparotomy showed a new stump leak, and a right hemicolectomy with terminal ileostomy was inevitable. Peritoneal fluid aspirate cultures were positive for *E. coli* ESBL (Extended Spectrum Beta-Lactamase), *E. faecium*, and *Candida krusei*, requiring wide-spectrum antibiotic therapy. An endotracheal aspirate was also positive with the Xpert MTB/RIF® assay, confirming TB disease. The patient was successfully extubated and discharged after 7 weeks, and she continued ambulatory anti-TB treatment, oral anticoagulation, and prophylactic TMP-SMX and itraconazole. After 8 weeks, *Mycobacterium tuberculosis* grew up in culture from peritoneal fluid, stool, and endotracheal secretions.

According to the World Health Organization (WHO), TB disease remains a significant public health problem, with 10 million new cases and 1.4 million deaths worldwide in 2019. The proportion of patients with CGD who are diagnosed with TB disease varies across countries. In North America and Europe, TB is an unusual manifestation in CGD, found in < 2% of the patients [1]. However, in endemic areas, patients with CGD are at high risk of TB disease [2]. In Mexico, Iran, and Turkey, up to 29%, 31%, and 42% of patients with CGD, respectively, were diagnosed with TB disease [1, 3]. However, XR and AR CGD patients can present with more complicated clinical course, including extrapulmonary and disseminated TB disease [1, 2]. The increase of frequency and severity of TB disease and BCG infection in CGD patients from developing countries suggest an essential contribution of the NADPH oxidase activity in the immunity against mycobacteria, in macrophages in particular [4]. The relation between TB and the residual or null activity of the NADPH oxidase in CGD has been previously established [4].

The last global WHO tuberculosis report describes that extrapulmonary TB represents about 15% of all TB forms,

while abdominal TB represents approximately 10% of extrapulmonary forms. Abdominal TB includes the mesenteric lymph nodes, peritoneum, gastrointestinal tract, and solid organs involvement [5]. A combination of these findings usually occurs in an individual patient [5], as in the present case. TB in the abdomen can be caused by the ingestion of tuberculous mycobacteria in the sputum or milk, by hematogenous or lymphatic spread from an active tubercular focus, or by direct spread into the peritoneum from adjacent infected organs such as the fallopian tubes [5]. The described case presented with abdominal TB involving the peritoneum, ovarium, and the intestine, concomitantly with pulmonary TB.

Early diagnosis of extrapulmonary forms of TB to promptly initiate adequate treatment is essential to prevent complications [5]. Moreover, clinical samples in abdominal TB are paucibacillary, decreasing diagnostic tests' sensitivity such as microscopy and culture [6]. Acid fast bacilli staining is positive in less than 3% of patients, and culture growth is positive in 20% of cases [5]. Since 15–25% of abdominal TB cases have concomitant pulmonary involvement, [5] pulmonary assessment of TB disease helps the diagnosis. Molecular biology techniques such as Xpert MTB/RIF assay® increase paucibacillary disease sensitivity, detecting as few as 10 mycobacteria [6]. However, it may not distinguish between *M. tuberculosis*, *M. bovis*, and *M. bovis*–BCG; all are members of the complex and possible causal agents of disease in CGD. Early diagnosis can prevent surgical intervention in abdominal TB, commonly indicated for acute complications [5]. In the patient reported here, the indication for surgery was intestinal perforation; however, this led to surgical complications and prolonged hospitalization. Finally, there is limited information about the most appropriate treatments for TB disease in CGD [2]. TB treatment in CGD does not differ from standard regimens, which are based on several drugs, including isoniazid, rifampin, pyrazinamide, and ethambutol during the intensive phase, followed by isoniazid and rifampicin during the continuation phase [5]. However, due to a higher susceptibility to mycobacterial disease in CGD, a more prolonged therapy must be considered, with a daily therapy to reduce the risk of relapse and drug resistance and surveillance with imaging and cultures [6]. This report highlights TB disease as a differential diagnosis of infection in patients with CGD, especially in endemic areas, highlighting the importance of timely diagnosis and prompt therapeutic interventions as critical factors in controlling the disease.

Author Contribution X.L.L., S.B.D., J.B., and L.B.G. performed or provided supervision of Sanger sequencing, and wrote the manuscript. A.C.M., P.L.C., A.T.M., N.S.N., and J.D.M. evaluated, diagnosed, and treat the patient. All authors commented on and discussed the paper and approved the final manuscript as submitted.

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Declarations

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Consent for Publication The patient has consented to the submission of the case report to the journal.

Competing of Interests The authors declare no competing interests.

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