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CASE REPORT

Multifocal Tuberculosis Revealing Chronic Granulomatous Disease in a Child: A Case Report and Review of the Literature

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KEYWORDS

Chronic granulomatous disease;

Inborn error of immunity;

Phagocyte dysfunction;

Multifocal tuberculosis;

Pediatric tuberculosis;

NADPH oxidase deficiency;

Dihydrorhodamine assay;

Hematopoietic stem cell transplantation

Abstract

Background: Chronic granulomatous disease (CGD) is a rare inherited inborn error of immunity caused by defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, resulting in impaired reactive oxygen species production and defective intracellular killing of microorganisms. Although recurrent bacterial and fungal infections represent the classical phenotype, *Mycobacterium tuberculosis* is increasingly recognized as a clinically relevant pathogen in tuberculosis-endemic regions. Multifocal tuberculosis as the initial manifestation of CGD remains rare and may substantially delay diagnosis.

Case Presentation: We report a 12-year-old Algerian boy born to second-degree consanguineous parents who presented with recurrent pleuropulmonary infections, severe growth failure, hepatosplenomegaly and multifocal tuberculosis involving the thoracolumbar spine, pleural and psoas muscle. Despite prolonged antituberculous therapy, he developed recurrent pleural effusions and persistent inflammatory disease. The combination of recurrent respiratory infections, generalized lymphadenopathy, hepatosplenomegaly, growth failure and parental consanguinity prompted investigation for an underlying inborn error of immunity. Functional assessment of neutrophil oxidative burst using the dihydrorhodamine (DHR) assay confirmed CGD. Antibacterial and antifungal prophylaxis was initiated, and the patient was referred for hematopoietic stem cell transplantation evaluation.

Conclusion: This case broadens the recognized infectious spectrum of CGD and highlights the need to consider CGD in children presenting with severe or multifocal tuberculosis associated with recurrent infections or other warning signs of immunodeficiency. Earlier diagnosis may facilitate timely prophylaxis, genetic counselling and referral for curative transplantation.

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Introduction

Chronic granulomatous disease (CGD) is a rare inherited inborn error of immunity (IEI) caused by defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, leading to impaired production of reactive oxygen species (ROS) and defective intracellular killing of microorganisms. Classically, the disease is characterized by recurrent bacterial and fungal infections, granuloma formation and chronic inflammatory complications affecting multiple organs (1–4).

The clinical spectrum of CGD is remarkably heterogeneous. Recurrent pneumonia, suppurative lymphadenitis, skin and liver abscesses, osteomyelitis and invasive aspergillosis constitute the most frequently reported manifestations, whereas inflammatory complications involving the gastrointestinal, respiratory and genitourinary tracts have become increasingly recognized over the past decade (2–4). In contrast, *Mycobacterium tuberculosis* has traditionally been considered an uncommon pathogen in CGD, and severe mycobacterial disease has long been regarded as more suggestive of inherited defects affecting the IL-12/IFN- γ pathway than disorders of phagocyte function (5,6).

This traditional concept has recently been challenged by accumulating reports from tuberculosis-endemic countries describing pulmonary, lymph node, osteoarticular and disseminated tuberculosis in patients with CGD (5,8–11). These observations suggest that the infectious phenotype of CGD may be influenced not only by the underlying molecular defect but also by environmental exposure and regional epidemiology. Consequently, tuberculosis should no longer be viewed as an exceptional finding in children with CGD, particularly in populations with a high burden of tuberculosis and frequent parental consanguinity.

Herein, we report the case of a child in whom multifocal tuberculosis involving the spine, pleura and psoas muscle revealed previously unrecognized CGD. Through comparison with contemporary international cohorts and the first Algerian multicenter experience, we discuss the evolving relationship between CGD and *M. tuberculosis* and highlight the diagnostic and therapeutic implications of this uncommon presentation.

Case Presentation

A 12-year-old Algerian boy was referred to the Department of Pediatrics A, Issad Hassani University Hospital (Béni Messous, Algiers), for evaluation of persistent hepatosplenomegaly associated with recurrent pleuropulmonary disease. He was born at term to second-degree consanguineous parents after an uncomplicated pregnancy and delivery. He had two healthy brothers, including a twin brother, and one healthy sister. There was no known family history of primary immunodeficiency, recurrent severe infections or early childhood deaths. Routine childhood immunizations, including Bacillus Calmette–Guérin (BCG), had been administered according to the national immunization schedule.

At 10 years of age, he developed progressive dorsolumbar pain with abdominal distension. CT and MRI demonstrated tuberculous spondylo discitis involving T12–L1 and L1–L2, complicated by vertebral collapse, a right psoas abscess and a small right pleural effusion. Histopathological examination of the drained psoas abscess showed caseous necrosis, supporting spinal tuberculosis. Antituberculous therapy was initiated, with transient clinical improvement.

Two years later, he developed progressive dyspnea and recurrent abdominal distension. Thoraco-abdominal CT revealed right upper lobe and paracardiac consolidation, a large right pleural effusion, marked hepatosplenomegaly and multiple abdominal lymphatic nodes. On admission, he had severe growth retardation (weight 24 kg, <–3 SD; height 123 cm, <–3.7 SD), massive hepatomegaly, stage III splenomegaly, right cervical and left inguinal lymphadenopathy, thoracolumbar kyphoscoliosis, right-sided exophthalmos and right hydrocele. Respiratory examination showed tachypnea and signs of right pleural effusion, without neurological deficit or hemodynamic instability.

Laboratory investigations revealed microcytic anemia (hemoglobin 9.4 g/dL, mean corpuscular volume 62 fL), thrombocytosis ($544 \times 10^9/L$) and elevated C-reactive protein (56 mg/L). Blood cultures were sterile, and serological testing for human immunodeficiency virus, hepatitis B virus and hepatitis C virus was negative. Diagnostic thoracentesis showed a lymphocyte-predominant exudative pleural effusion with negative routine bacterial cultures.

The association of recurrent respiratory infections, multifocal tuberculosis, persistent hepatosplenomegaly, generalized lymphadenopathy, severe growth failure and parental consanguinity prompted evaluation for an underlying inborn error of immunity. Functional assessment of neutrophil oxidative burst using the DHR assay demonstrated a markedly impaired oxidative burst, confirming CGD. Molecular genetic analysis is ongoing.

After diagnosis, trimethoprim-sulfamethoxazole and itraconazole prophylaxis were initiated. HLA typing was performed in the patient and his siblings to assess eligibility for allogeneic hematopoietic stem cell transplantation. The hospital course was complicated by recurrent right pleural effusions requiring therapeutic thoracenteses, severe anemia requiring red blood cell transfusion and secondary pleural infection due to extended-spectrum β -lactamase-producing requiring escalation to imipenem and amikacin. Persistent pleural disease led to surgical drainage and pleural biopsy, which showed chronic granulomatous inflammation with extensive caseous necrosis. Antituberculous therapy was reintroduced according to the national protocol while CGD prophylaxis was maintained.

Discussion

CGD is classically characterized by recurrent bacterial and fungal infections caused by catalase-positive microorganisms, whereas *Mycobacterium tuberculosis* has traditionally been regarded as an uncommon pathogen (1–4). This concept was largely established from European and North American cohorts, where invasive aspergillosis and pyogenic bacterial infections account for most severe infectious complications (2,7). Consequently, tuberculosis has generally been considered more suggestive of inherited defects affecting the IL-12/IFN- γ pathway than disorders of phagocyte function (5,6).

Accumulating evidence from tuberculosis-endemic countries has challenged this paradigm. Studies from Egypt, Morocco and Turkey have documented pulmonary, lymph node and osteoarticular tuberculosis in children with CGD, suggesting that *M. tuberculosis* is probably underrecognized in these populations (8–10). Likewise, the first Algerian multicenter cohort reported by Saddjaballah et al. identified *M. tuberculosis* among the documented pathogens, supporting the concept that tuberculosis represents a clinically

relevant component of the infectious spectrum of CGD in Algeria (11).

Our patient illustrates this evolving phenotype. Multifocal tuberculosis involving the spine, pleura and psoas muscle dominated the initial clinical presentation and delayed recognition of the underlying immunodeficiency. Rather than representing an incidental association, this observation supports the growing evidence that tuberculosis should be considered among the possible manifestations of CGD in endemic regions, particularly when associated with recurrent respiratory infections, hepatosplenomegaly, growth failure or parental consanguinity.

The mechanisms underlying susceptibility to *M. tuberculosis* in CGD are increasingly understood. Beyond their direct antimicrobial activity, reactive oxygen species generated by the NOX2 complex regulate phagosome maturation, autophagy, inflammasome activation and granuloma organization (3,4,12). Consequently, defective oxidative burst results in both impaired intracellular bacterial clearance and dysregulated inflammatory responses. This dual mechanism probably explains the persistent vertebral and pleural granulomatous inflammation observed in our patient despite prolonged antituberculous therapy and supports the concept that CGD is not only a disorder of defective microbial killing but also a disease of immune dysregulation (3,4).

Defective ROS production alone, however, cannot fully explain the geographical variability observed among published cohorts. Environmental exposure to *M. tuberculosis*, widespread BCG vaccination and delayed diagnosis probably contribute to the increasing recognition of tuberculosis-associated CGD in endemic regions. While invasive aspergillosis remains the dominant opportunistic infection in European and North American registries, tuberculosis appears increasingly represented in cohorts from North Africa and the Middle East (2,7–11).

Comparison with the first Algerian multicenter cohort reported by Saddjaballah et al. provides additional insight (11). Similar to the national cohort, our patient presented with pulmonary involvement, hepatosplenomegaly and parental consanguinity. However, his diagnosis was established considerably later, and the combination of vertebral tuberculosis, psoas abscess and recurrent pleural disease represents a particularly severe presentation. This observation expands the phenotypic variability described in

Algerian children with CGD and highlights the consequences of delayed diagnosis.

The present case highlights the importance of considering CGD whenever severe or multifocal tuberculosis is associated with recurrent bacterial infections, persistent inflammatory manifestations or parental consanguinity. Under these circumstances, early functional assessment of neutrophil oxidative burst using the DHR assay should be performed to avoid diagnostic delay (1,3,4).

Confirmation of CGD has immediate therapeutic implications. Long-term prophylaxis with trimethoprim-sulfamethoxazole and antifungal therapy remains the cornerstone of management, while early referral for hematopoietic stem cell transplantation is recommended for eligible patients because transplantation performed before irreversible organ damage is associated with excellent long-term outcomes (13,16,17). Our patient's clinical course illustrates the consequences of delayed diagnosis, with irreversible vertebral damage and chronic pleuropulmonary disease already established before appropriate prophylactic and curative strategies could be implemented.

Taken together, this case emphasizes that improving outcomes in CGD depends not only on advances in treatment but also on earlier recognition of atypical clinical presentations. In tuberculosis-endemic countries, multifocal tuberculosis should prompt systematic evaluation for an underlying inborn error of immunity, particularly when additional clinical or familial warning signs are present.

Conclusion

This case broadens the recognized clinical spectrum of CGD by illustrating that multifocal tuberculosis may represent its presenting manifestation in children living in tuberculosis-endemic regions. Beyond its clinical rarity, this observation emphasizes that severe or atypical tuberculosis should not systematically be regarded as an isolated infectious disease, particularly when associated with recurrent bacterial infections, hepatosplenomegaly, growth failure or parental consanguinity.

Our findings further support the emerging concept that the infectious phenotype of CGD is shaped not only by the underlying genetic defect but also by regional epidemiology and environmental exposure. Integrating this perspective into clinical

practice is essential to reduce diagnostic delay and to ensure timely antimicrobial prophylaxis and evaluation for hematopoietic stem cell transplantation before irreversible infectious and inflammatory complications develop.

Finally, this report, interpreted in the context of both the international literature and the first Algerian multicenter experience, highlights the importance of increasing awareness of inborn errors of immunity among clinicians managing childhood tuberculosis. Earlier recognition of these disorders will improve individual outcomes and contribute to a better understanding of the geographical variability and expanding phenotype of CGD.

Déclaration d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêt.

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