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Chronic Granulomatous Disease: A Perspective from a Developing Nation

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Dear Editor,

We read with great interest the article by Aygun et al. [1] on a Turkish cohort of 32 patients with chronic granulomatous disease (CGD) who were diagnosed in a tertiary care facility over the period of 12 years. Authors have given a comprehensive overview of clinical, immunological, and molecular features of CGD and highlighted that X-linked subtype is more common than autosomal recessive (AR) forms of CGD in their cohort. Patients with X-linked CGD presented earlier than those with AR-CGD, and median diagnostic delay was 12 months (X-linked:11.5; AR:12). Non-infectious complications included anaemia (68.8%) and failure to thrive (59.4%) and 2 patients had inflammatory bowel disease. All patients received trimethoprim-sulfamethoxazole and itraconazole prophylaxis, and 4 patients underwent successful allogenic haematopoietic stem cell transplantation (HSCT).

In this cohort where the median age of diagnostic delay was 12 months, it will be helpful for readers if the authors could enumerate the reasons for diagnostic delay in their cohort. Barkai et al. [2] recently reported a cohort of 16 patients from Israel who were diagnosed with CGD in their adulthood with median diagnostic delay of 19.25 years. The authors report that many patients in their cohort were initially labelled with tuberculosis, sarcoidosis, Behcet's disease, or inflammatory bowel disease before the diagnosis of CGD was made. We, at our centre in North India, have diagnosed 80 patients with CGD in the last 25 years and many patients with CGD have been misdiagnosed as tuberculosis and were given empirical antitubercular therapy (ATT) before a correct diagnosis was made.

Our first patient was diagnosed in the year 1994 at our centre in North India and was in a long-term follow up with us [3, 4]. He was referred to our institute for evaluation of persistent pneumonia and failure to thrive at the age of 1.5 years in August 1993 (Fig. 1a). He had been initiated empirically on ATT from outside. On examination, he had pallor, bilateral cervical and axillary lymphadenopathy, tachypnoea, crepitations in the right lung field, and hepatosplenomegaly. Tuberculin skin test and gastric and bronchoalveolar lavage for acid-fast bacilli were negative. Blood fungal culture revealed growth of *Aspergillus fumigatus*. He was treated with intravenous amphotericin for 2 weeks and was continued on ATT. In February 1994, he was admitted with pneumonia and microbiological investigations revealed growth of *Candida albicans* in lung parenchymal aspirate. Work up for tuberculosis was again negative. Serum protein electrophoresis revealed hypergammaglobulinemia. Nitro blue tetrazolium (NBT) test showed no reduction, and a diagnosis of CGD was

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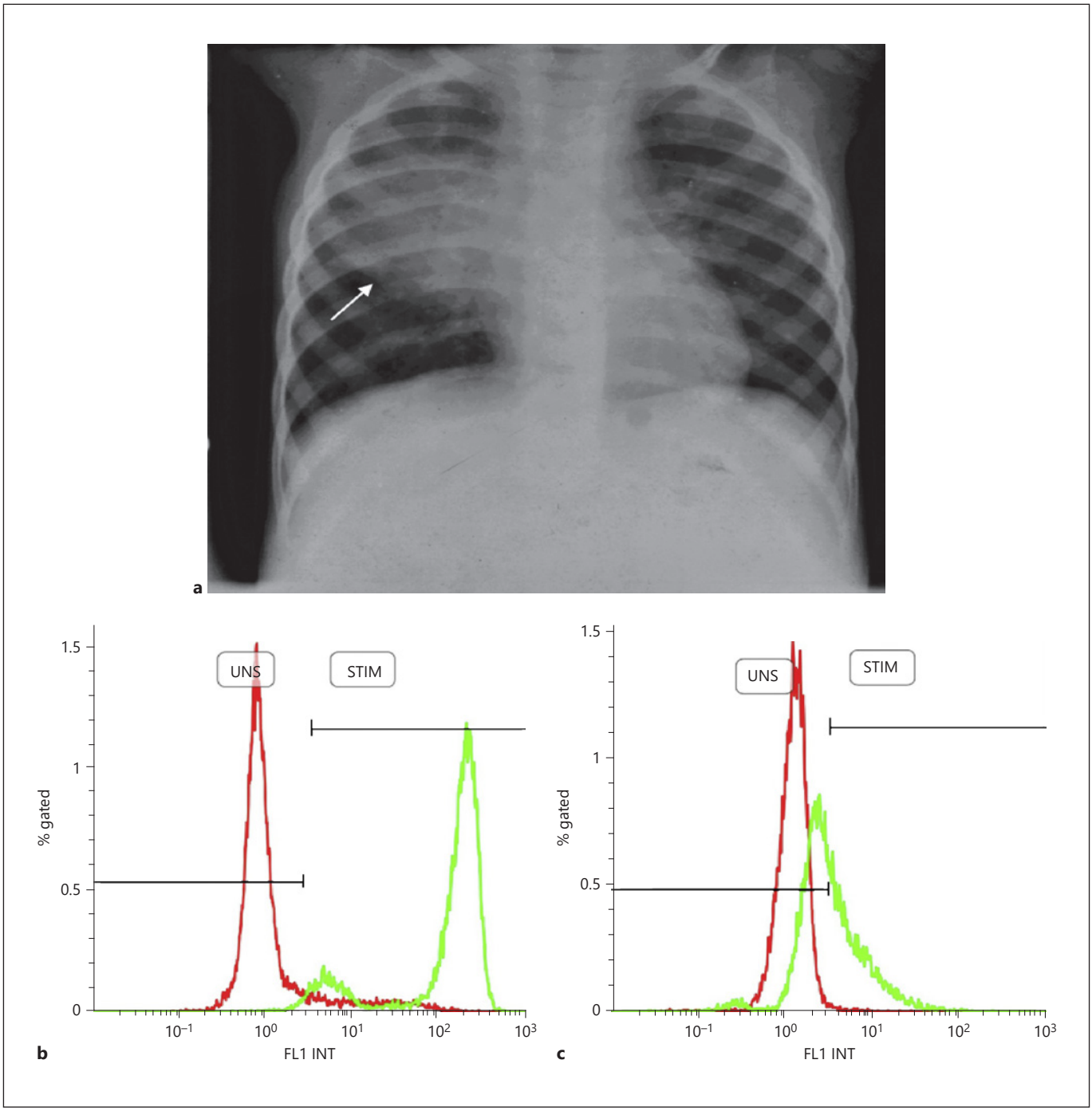

Fig. 1. Anteroposterior view of chest radiograph showing right upper lobe consolidation (**a**); DHR assay by flow cytometry in healthy control showing MFI in PMA stimulated neutrophils of 222 × 41 (unstimulated – 2 × 75) and stimulation index† (SI) of 80 × 87 (**b**); DHR assay by flow cytometry in the index case showing MFI in PMA stimulated neutrophils of 2 × 86 (unstimulated – 1 × 27) and SI of 2 × 25, suggestive of CGD †SI calculated from the MFI of stimulated neutrophils divided by MFI of unstimulated neutrophils (**c**). DHR, dihydrorhodamine; MFI, median fluorescent intensity; PMA, phorbol-myristate acetate; CGD, chronic granulomatous disease.

proffered. He received intravenous amphotericin for 2 weeks followed by oral itraconazole for 2 months in therapeutic dosages. He was subsequently started on oral cotrimoxazole (5 mg/kg of trimethoprim) and itraconazole (100 mg) daily for prophylaxis. The second patient was his elder sister who also had repeated episodes of pneumonia since early childhood and was empirically treated with multiple courses of ATT for many years until she was finally diagnosed with CGD at the age of 9 years. However, she had established bronchiectasis when she was diagnosed and succumbed to severe pneumonia at 14 years of age despite cotrimoxazole and itraconazole prophylaxis.

The boy continued to remain well after initiation of prophylaxis and he did not develop any infective or inflammatory complications after that. His compliance to antimicrobial prophylaxis was checked every 6 months in his follow-up visit to our paediatric immunodeficiency clinic. He completed his high school and later also received a bachelor degree. Our institute started performing dihydrorhodamine (DHR) test by flow cytometry from 2011. The patient's DHR was suggestive of CGD (Fig. 1b, c). Genetic diagnosis of CGD was established subsequently; *NCF1*, c.73_74delGT identified by gene scan technique [4]. Currently, he is 27 years old, keeping good health, and is gainfully employed.

The above experience created awareness amongst the physicians to suspect and investigate for CGD in patients with clinical presentation such as tuberculosis (prolonged fever, pneumonia, and failure to thrive) where there is no microbiological evidence for *Mycobacterium tuberculosis*. Over the years, we have observed that the rates of misdiagnosis of tuberculosis, empirical initiation of ATT, and diagnostic delay in patients with CGD have drastically come down. We reiterate that the most important part in diagnosis of CGD is early clinical suspicion and it can be supplemented by a simple diagnostic test such as NBT. Hence, the reasons for diagnostic delay will provide clues for early suspicion of CGD amongst clinicians and this would ultimately result in increased awareness of the condition.

Though the authors have described the type and aetiology of infections in all patients, it would be more helpful for clinicians if the frequency and type of infections before and after initiation of antimicrobial prophylaxis could be provided. The information would be helpful to assess the efficacy of prophylactic medications in reducing the frequency of infections. Microbiological spectrum of infections can also be different post initiation of prophylactic medications [5]. Long-term follow-up of patients with CGD is essential to understand the natural course of disease, ensure compliance with medications, and to assess need for HSCT. Authors have mentioned the outcome of patients in their cohort; however, the duration of follow-up and information on compliance to medications were not available.

Hyperinflammation in CGD often requires oral corticosteroids and managing such complications can be challenging if there is associated infection. Use of glucocorticoids in liver abscess in CGD has also shown to have improved rates of resolution and decreased requirement of surgical intervention [6]. However, authors have not mentioned the management of non-infective or inflammatory complications in their cohort. Moreover, the cause for hypereosinophilia noted in 8 patients and their management is also not clear. If authors could provide information regarding these aspects, this would be helpful for clinicians managing such complications. Authors have also reported successful outcomes of HSCT in 4 patients who are transplanted with HLA-matched donors with reduced intensity conditioning. However, if more details of HSCT such as waiting period, financial support for the families to undergo HSCT, drugs used for conditioning, prophylaxis used for graft-versus-host disease, and graft manipulation techniques are provided, this would be helpful for centres which are naïve in transplanting these patients.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest Statement

All authors declare that he/she has no potential conflict of interest.

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Author Contributions

S.L.: writing of initial draft of the manuscript, editing, and revision of manuscript at all stages of its production, and review of the literature. P.V.: inception of the manuscript's idea and editing, critical revision of the manuscript at all stages of production, and final approval. R.K.P.: editing the manuscript. A.R.: laboratory support and editing the manuscript. S.S.: patient management and final editing of the manuscript. Competing interest for all authors: no financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Consent to Participate

Informed written consent was taken from parents of patient included in the report.

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