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CASE STUDY

CHRONIC SEPTIC GRANULOMATOSIS REVEALED IN ADULTHOOD BY RESPIRATORY MANIFESTATIONS

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ABSTRACT

Chronic Granulomatous Disease (CGD) is a rare hereditary immune disorder characterized by impaired phagocyte cell function, resulting in recurrent respiratory infections. While primarily observed in young children, it occasionally presents in adults. Here, we report two cases diagnosed at the Respiratory Diseases Department of ibn Rochd University Hospital, highlighting the manifestation of CGD in adulthood through respiratory symptoms. The first case involves a 20-year-old patient with recurrent fistulated adenitis and purulent pleurisy, leading to the diagnosis of CGD. In the second case, a 28-year-old patient with a history of recurrent respiratory infections presented with invasive aspergillosis, prompting the diagnosis of CGD. Our study underscores the importance of considering immunodeficiency in the context of recurrent respiratory infections, even in adulthood. It emphasizes the need to suspect CGD in patients with invasive aspergillosis, particularly in the absence of a significant medical history. By shedding light on these observations, we aim to raise awareness among clinicians about the potential presentation of CGD in adults and the importance of early diagnosis and intervention in managing respiratory manifestations associated with this condition, especially it is a diagnosis that is frequently overlooked by pulmonologists.

Keywords: Ergillosis; Chronic septic granulomatosis; Adulthood

АБСТРАКТ

Хроническая гранулематозная болезнь (ХГБ) - редкое наследственное иммунное заболевание, характеризующееся нарушением функции клеток-фагоцитов, что приводит к рецидивирующим респираторным инфекциям. В основном оно наблюдается у детей младшего возраста, но иногда встречается и у взрослых. Здесь мы сообщаем о двух случаях, диагностированных в отделении респираторных заболеваний университетской больницы ibn Rochd, и подчеркиваем проявление КГД во взрослом возрасте через респираторные симптомы. В первом случае речь идет о 20-летнем пациенте с рецидивирующим свищевым аденитом и гнойным плевритом, что привело к постановке диагноза ХГД. Во втором случае у 28-летнего пациента с рецидивирующими респираторными инфекциями в анамнезе был инвазивный аспергиллез, что послужило поводом для постановки диагноза ХГД. Наше исследование подчеркивает важность рассмотрения иммунодефицита в контексте рецидивирующих респираторных инфекций, даже в зрелом возрасте. Оно подчеркивает необходимость подозревать наличие ХГД у пациентов с инвазивным аспергиллезом, особенно при отсутствии значимого анамнеза. Проливая свет на эти наблюдения, мы стремимся повысить осведомленность клиницистов о потенциальной презентации ХГД у взрослых и важности ранней диагностики и вмешательства в лечение респираторных проявлений, связанных с этим состоянием, особенно это диагноз, который часто упускается из виду пульмонологами.

Ключевые слова: Эргиллез; Хронический септический гранулематоз; взрослая жизнь

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INTRODUCTION

Chronic septic granulomatosis is a rare genetic disease that affects the immune system. It is characterized by a primary immune deficiency that makes it more difficult for phagocytic cells (such as polymorphonuclear neutrophils, eosinophils, monocytes, and macrophages) to eradicate some harmful bacteria and fungi. It is considered an orphan disease because it affects less than 0.05% of a given population.

MATERIAL AND METHODS

First observation, Mr. A.H., a 20-year-old individual, has a medical history of recurring fistulized adenitis that resolves on its own. He has been experiencing shortness of breath during physical activity, pain on the right side of his chest, and a dry cough for one month prior to being admitted. During the physical examination, we observed a condition characterized by the accumulation of fluid in the bottom one-third of the right side of the chest cavity. We identified a right pleural opacity on the chest x-ray (Figure 1).

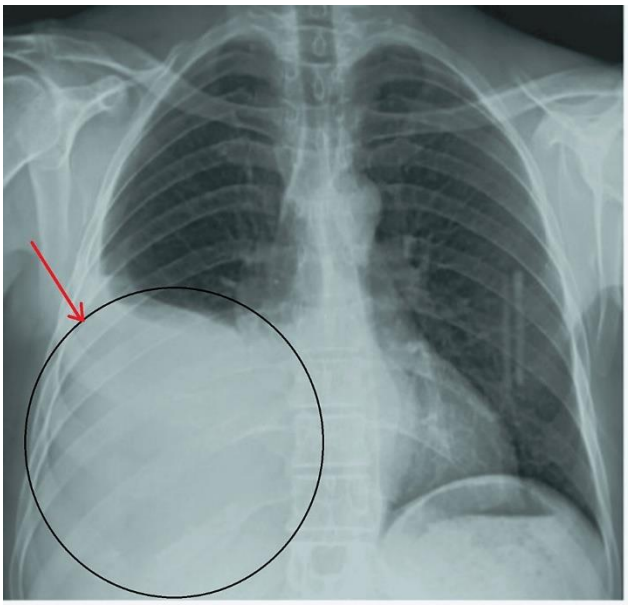

Figure 1: A radiograph of the chest displaying an area of increased density in the pleural region, indicative of purulent pleurisy.

During the exploratory pleural puncture, the presence of purulent pleurisy was noted. The pleura was thin because a cytological analysis showed that polymorphonuclear neutrophils (PNN) were present 80% of the time. The patient underwent a pleural cavity evacuation, removing a total of 8 liters of fluid. They received dual antibiotic therapy consisting of amoxicillin and clavulanic acid at a dosage of 3 grams per day and ciprofloxacin at a dosage of 1 gram per day. During the field evaluation, all serologies yielded negative results, and the protein electrophoresis showed no significant findings. At the Department of Medical Diagnosis (DMD), the file was looked at, and it was decided that chronic septic granulomatosis could be the diagnosis because of the recurring fistulized lymphadenitis. The patient received a nitroblue tetrazolium (NBT) test, which successfully confirmed the diagnosis. To start preventing infections, the team mixed the antibiotic trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim®) with the antifungal drug itraconazole. Daily evacuations and respiratory therapy were part of this treatment regimen. The progression after 6 weeks was characterized by favorable clinical and radiological improvement, particularly the resolution of pleurisy (Figure 2). Because respiratory fungal infections in adults rarely cause symptoms, the patient is constantly under observation at our facility.

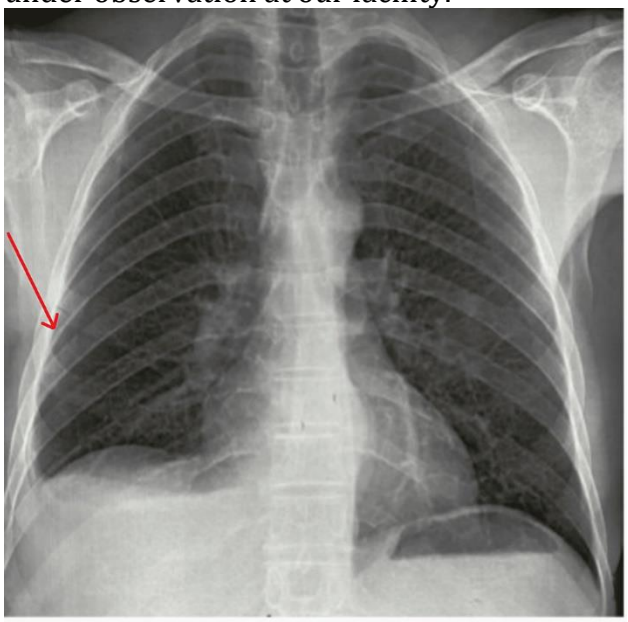

Figure 2: A radiograph of the chest reveals the total resolution of pleurisy following treatment and evacuations.

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Second observation, Mr. H.K., a 28-year-old individual with a medical background of recurrent respiratory and ear, nose, and throat infections, has been experiencing a persistent bronchial syndrome with pus-like discharge for the past 2 months. There is breathing difficulty when exercising, and this condition has not responded to conventional antibiotic treatment. Additionally, Mr. H.K. has been experiencing feverish sensations, night sweats, and a decline in overall health. During the clinical examination, we detected bilateral rumbling rales. Additionally, the chest x-ray revealed scattered opacities resembling alveoli in the upper two-thirds of both hemi thoraxes (Figure 3).

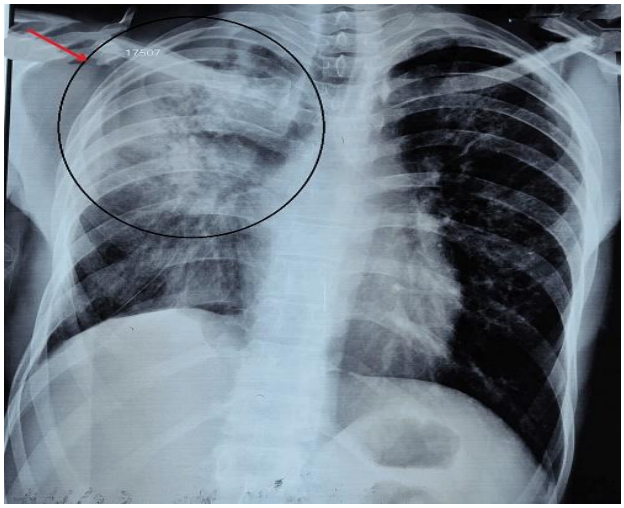

Figure 3: The face radio thorax reveals an alveolar opacity occupying the upper portion of the right hemithorax.

The patient received a chest CT scan that detected a region of pneumonia (Figure 4).

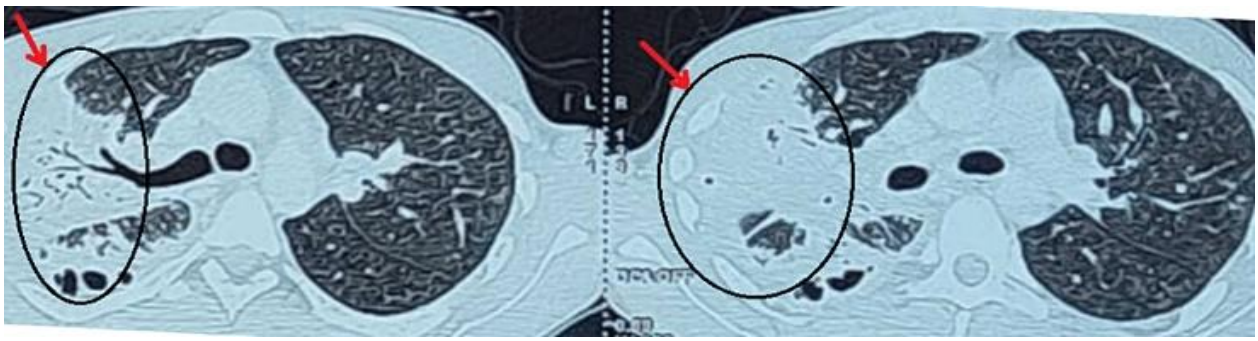

Figure 4: A thoracic scanner that shows an airflow obstruction with an overhead bronchogram at the top lobes.

Sputum from the patient was analyzed as part of the diagnostic process in order to ascertain whether or not the Xpert gene was present in the patient's body. It was determined that the examination yielded negative results. The findings of the tests for HIV, HVC, HVB, and syphilis serology were all negative. In addition, the results of both tests were negative. Antibiotic medication was delivered to the patient; nevertheless, there was no visible change in the patient's condition that was seen after the treatment was administered. During their time in the hospital, the patient experienced a painful red eye as well as a decrease in their vision. All of these symptoms occurred simultaneously. As a result of this, the patient sought the advice of an ophthalmologist, who diagnosed the patient with chorioretinitis. This finding led to the conclusion that the patient may be suffering from ocular aspergillosis. There was a positive result obtained from the aspergillus serology test that he underwent. After reviewing the file at the Department of Medical Diagnosis (DMD), it was decided to conduct an investigation into the patient's medical history as well as their current symptoms in order to determine whether or not there is a possible underlying cause.

RESULT

The diagnosis of chronic septic granulomatosis is established through the utilization of the NBT test. Therapeutically, he

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is undergoing therapy with an antifungal medication called Itraconazole as well as a combination of an antibacterial medication called trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim®) for infection prevention, exhibiting favorable clinical and radiological progress (Figure 5).

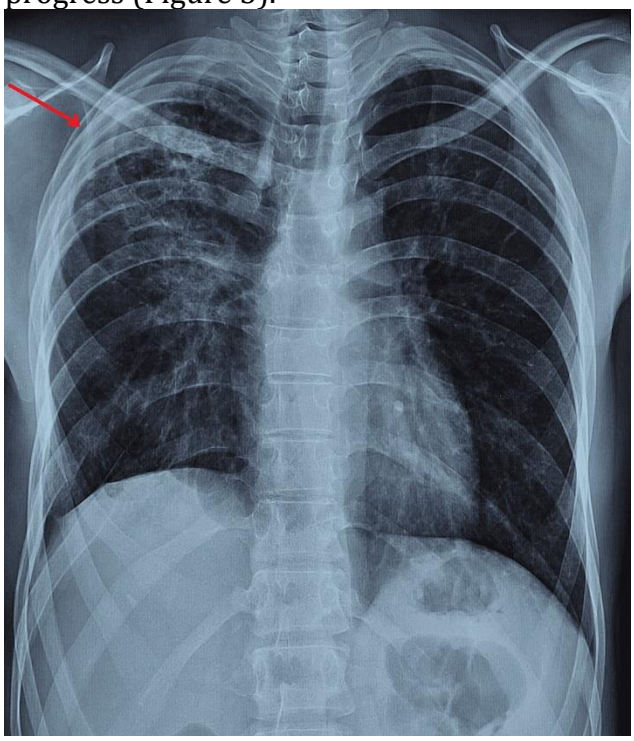

Figure 5: After anti-parasitic treatment, a face thoracic x-ray shows a rudimentary cleaning.

The optimal therapy for individuals with septic granulomatosis is allograft transplantation. Regrettably, we have not yet identified suitable donors for our patients, particularly given the recent use of the diagnostic procedure.
The aim of this study is to describe and delineate the specificities of pulmonary manifestations in adult patients with Chronic Granulomatous Disease (CGD). It is noteworthy that bacterial infection exhibited significantly more symptoms compared to fungal infections. A particular characteristic of these fungal infections is their loco-regional extension involving the thoracic wall but lacking angioinvasion, resulting in the absence of nodules with halos on thoracic CT scans. It is imperative to screen for infectious complications in patients with chronic granulomatous disease; however, in our two patients, the diagnosis of CGD was made following their persistent infection. We have focused particularly on describing respiratory manifestations in adulthood, which may contribute to an underestimation of events during childhood.

DISCUSSION

Chronic septic granulomatosis (CSG) is an uncommon inherited immune disorder that was initially identified in the 1950s. This happens because of a change in the genes that control parts of NADPH oxidase. This makes oxidative metabolism harder and stops immune cells from getting rid of pathogens that they have taken in.[1] The occurrence of numerous infections and persistent inflammatory responses, which primarily affect the lungs, distinguish this condition. Pneumonia is a frequent occurrence in people with GSC. Staphylococcus aureus, Aspergillus species, and Burkholderia cepacia are commonly responsible for bacterial infections. Repeated viral outbreaks and ongoing inflammation that affects multiple organs are characteristics of the disease.[2]

Infections persist as the primary symptoms of the disease, even with the use of anti-infectious prophylaxis. They exhibit premature, many, and occasionally intense characteristics. All the series show that pulmonary infections are the most common type. Other common types are suppurative lymphadenopathy, deep abscesses (subcutaneous, hepatic, etc.), osteomyelitis, and bacteremia.[3]

Fungal infections are highly prevalent, occurring early and exhibiting severe symptoms. In the French CEREDIH series, 42.6% of all patients and 75% of individuals over the age of 30 experienced at least one episode of invasive fungal infection (IFI) throughout their lifetime.[4] These infections primarily affect the lungs, with 90.6% of cases occurring in the pulmonary region. Aspergillus fumigatus is the most identified species, although Aspergillus nidulans infections are common and primarily occur in individuals with chronic

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granulomatous disease (CGD). One notable clinical feature of these infections is their tendency to have few symptoms at the time of diagnosis. In the American NIH series, the proportion of patients with fever was only 20%.[5] Similarly, in a French series, out of 29 confirmed cases of invasive fungal infections, barely half of the patients showed indications of respiratory dysfunction, and only a third had a fever.[6]

Systematic chest imaging that reveals the presence of numerous nodules or masses frequently indicates the diagnosis. It is important to note that the halo sign around pulmonary nodules only appear very rarely in cases of aspergillosis that happen in people whose immune systems have been weakened by chemotherapy, like those who have had allograft bone marrow transplants. This rarity suggests a less common occurrence of angio-invasion and a more granulomatous progression. However, the spread of these sores to the chest wall and nearby organs appears to occur more often, especially in cases of Aspergillus nidulans infections. The sensitivity of serum galactomannan antigen detection for diagnosing invasive aspergillosis is quite low. Other microbiological procedures, such as the detection of 13βDglucan or PCR, have not been assessed in CGD. This sometimes requires the use of invasive diagnostic techniques. The procedures involved are bronchoalveolar cleaning and a lung biopsy.[7] In addition to infectious episodes, the disease's natural progression is characterized by chronic inflammatory symptoms, with the most common being the development of granulomas. Granulomas can develop in many organs and cause significant morbidity. Pulmonary inflammatory symptoms are present, but they have received limited attention and are likely to be overestimated in connection to infectious consequences.[8]

The diagnosis of CGD involves the comprehensive examination of phagocytic cells, specifically neutrophils, by functional, biochemical, and biomolecular analysis.[9] The primary diagnostic test is the nitroblue tetrazolium test, also known as the NBT test. NBT is a yellow dye that is engulfed by granulocytes simultaneously with the microbial agents or stimulants they encounter (such as endotoxin, staphylococcus, and PMA phorbol myristate acetate). Upon entering the phagosome, the NBT will undergo reduction by superoxide ions, resulting in the formation of an insoluble blue molecule. The process of enumerating cells that exhibit diminished NBT on a slide facilitates the identification of CGD illnesses. Occasionally, it becomes imperative to enhance the patient's immune system. In vitro, interferon γ (IFN-γ) enhances the activity of NADPH oxidase in monocytes.[10] When it comes to treating inflammatory symptoms, it is common to use corticosteroid therapy. Thalidomide has demonstrated efficacy in treating digestive and pulmonary symptoms in cases where corticosteroids are not useful. This treatment has been found to have minimal harm, as reported by Sokol in 2009 and Noel in 2013. The administration of alternative immunosuppressants or immunomodulators (such as cyclophosphamide, hydroxychloroquine, intravenous immunoglobulins, etc.) is determined on an individual basis, and in certain cases, surgery may be required.[11]

The curative therapy for the condition involves allogeneic bone marrow transplantation. Due to the high morbidity and mortality associated with this technique, it is only used for a small group of patients who have severe symptoms of infection or inflammation that do not respond to standard treatments.[12]

An alternative approach involves utilizing several probes that exhibit altered fluorescence in the presence of reactive oxygen species (ROS). These methods are conducted using whole blood, and the fluorescence is quantified by flow cytometry.

The utilization of Dihydrorhodamine123 (DHR) is notably dependable and uncomplicated, rendering it one of the benchmark methodologies. DHR readily infiltrates phagocytes simultaneously with the soluble substances they encounter and

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undergoes oxidation by H2O2, resulting in the formation of rhodamine123. Nevertheless, it is crucial to consider the occurrence of incorrect negative results when employing these procedures in instances of myeloperoxidase deficiency.[13] Confirmation of these functional tests can be achieved using biochemical and biomolecular assays that specifically target mutations or the synthesis of individual components of NADPH oxidase. Consequently, we shall conduct Western Blot studies to illustrate the synthesis of various glycoproteins or directly investigate for mutations in the genes encoding these components.[14]

The primary focus in managing CGD patients is the prevention of infectious episodes. The clinical presentation has significantly changed with the implementation of a systematic anti-infectious prophylactic regimen that combines the use of an antibacterial agent, trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim®), and an antifungal medication, itraconazole (Sporanox®). Regarding TMPSMX, no randomized study has been conducted; however, multiple retrospective studies indicate a decrease in the occurrence of serious infections when it is utilized. Early intervention is crucial in the management of infections. This necessitates frequent surveillance of patients, the utilization of frequently intrusive diagnostic methods, and the administration of broad-spectrum antimicrobial agents. Amphotericin B and voriconazole are the current standard therapies for fungal infections. In a study conducted by Segal et al. in 2005, the efficacy of posaconazole was demonstrated in eight patients with chronic granulomatous disease (CGD) who had shown resistance to voriconazole.[15]

CONCLUSIONS

Chronic septic granulomatosis is a long-term medical condition that has significantly advanced in terms of understanding, knowledge, and treatment over the past two decades. Presently, the challenges presented by this medical condition necessitate the provision of highly specialized and interdisciplinary healthcare. Patients afflicted with this condition experience a significantly enhanced life expectancy and quality of life, although they still face the risk of serious infections and inflammatory consequences that pose a hazard.

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DECLARATIONS

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Conflict of interest. This statement emphasizes the honesty and impartiality of the research process and guarantees openness in revealing any possible prejudices that could impact the accuracy of the study's findings.

Additional information. No additional information is available for this paper.

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