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Case Report

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Arthritis and Osteomyelitis due to *Aspergillus fumigatus*: A 17 years old boy with chronic granulomatous disease

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Abstract

Background: Invasive *Aspergillus* infections are frequently seen in immunocompromised patients but arthritis is a rare complication of *Aspergillus* infections in the absence of immune suppressive therapy, trauma or surgical intervention.

Case presentation: A 17 years old male patient with arthritis and patellar osteomyelitis of the left knee whose further investigations revealed chronic granulomatous disease as the underlying disease is followed. *Aspergillus fumigatus* was isolated from the synovial fluid and the tissue samples cultures. He was treated with Amphotericin B deoxicolate 0.7 mg/kg/day. Also surgical debridement was performed our patient. Amphotericin B nephrotoxicity developed and the therapy switched to itraconazole 400 mg/day. Itraconazole therapy were discontinued at the 6th month. He can perform all the activities of daily living including.

Conclusion: We think that, chronic granulomatous disease should be investigated in patients who have aspergillar arthritis and osteomyelitis.

Background

Aspergillus causes of infection in immunocompromised patients. In aspergillar arthritis, the immune system is found to be defective frequently. Chronic granulomatous disease (CGD) is the major underlying disease [1]. CGD is a 70 % X-linked recessive disease effecting especially the male patients and characterized by the impaired phagocyte microbicidal activity. Bacterial and fungal infections often begin during infancy and recur throughout childhood and adolescence [2–5].

Case Presentation

A 17 years old male patient referring to a private medical clinic with an arthritis at his left knee was given non steroidal anti-inflammatory therapy. As his arthritis continued, he was admitted to our hospital. In 1988, he had a craniotomy and a cerebral mass was excised but he had no further pathology reports concerning the excised material and he was continuing to take antiepileptic medications. In 1994 for pulmonary tbc, he had been given antituberculosis therapy for one year. He had no trauma or surgical intervention to his left knee. In his physical examination,

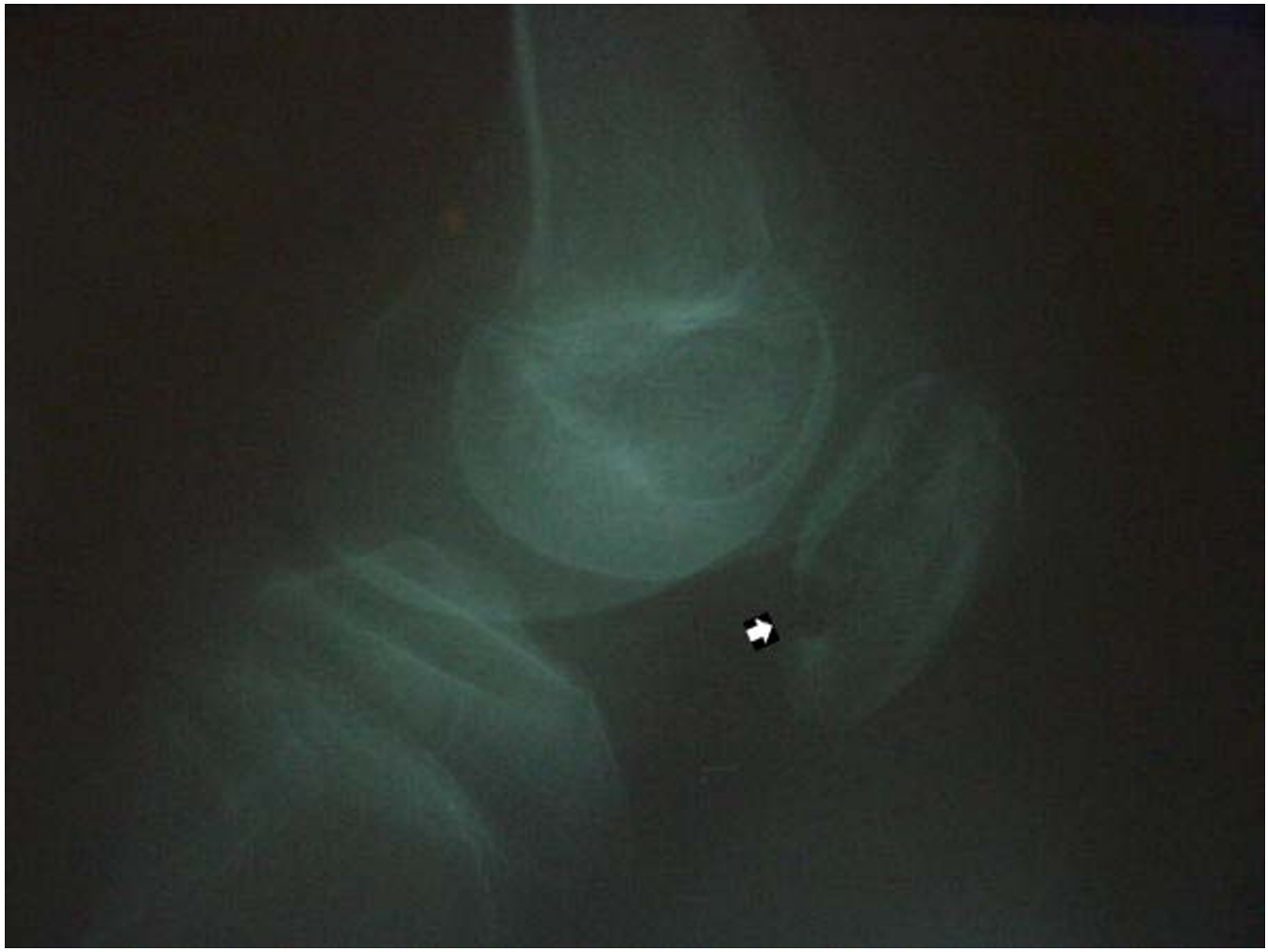

Figure 1
Left knee radiograph for patient with *Aspergillus* arthritis and osteomyelitis. A lytic lesion of the patella.

his body temperature was 39.2°C, multiple lymphadenopathy with different sizes at the axillar region, hepatosplenomegaly and arthritis at his left knee was detected. Laboratory examination revealed erythrocyte sedimentation rate (ESR) 86 mm/h, hemoglobin 9.5 gr/dl, leukocyte 5900 /mm3, thrombocyte 473 000/m3, CRP 221 mg/dl (normal < 5 mg/dl), Ig G 20.9 g/l (normal 7–16 g/l), Ig A 5.5 g/l (normal 0.7–4 g/l), Ig M 2.8 g/l (normal 0.4–2.3 g/l), albumin 24 mg/dl (normal > 35 mg/dl), PPD 20 mm diameter and HIV, rheumatoid factor and brucella agglutination tests were all negative. All the other biochemical tests were normal. X rays and magnetic resonance imaging (MRI) of the left joint showed septic arthritis (Figure 1) and patellar osteomyelitis (Figure 2). As the synovial fluid analysis displayed 80 % polymorphonuclear leukocytes, ceftriaxone 2 g/day and teicoplanin 400 mg/day were intitiated with the diagnosis of septic arthritis. His cranial MRI was normal except secondary findings due to his previous cranial operation. In the computerized tomography (CT) of the thoracal region, there were multiple lymph nodes at the axillary region and multiple calcified lymph nodes at the hilar region but bilateral pulmonary paranchimal regions were normal. The results of the blood cultures were negative. At the examination of synovial fluid, AARB was negative. *Aspergillus fumigatus* was isolated from the synovial fluid. Excisionel biopsies were taken from the left knee synovium and axillary lymph node. Histopathological examination of the left knee specimen expressed granulomatous lesion due to *Aspergillus* (Figure 3) and the lymph node biopsy from the axillary region showed changes compatible with the granulomatous disease. The patellar osteomyelitic tissue was surgi-

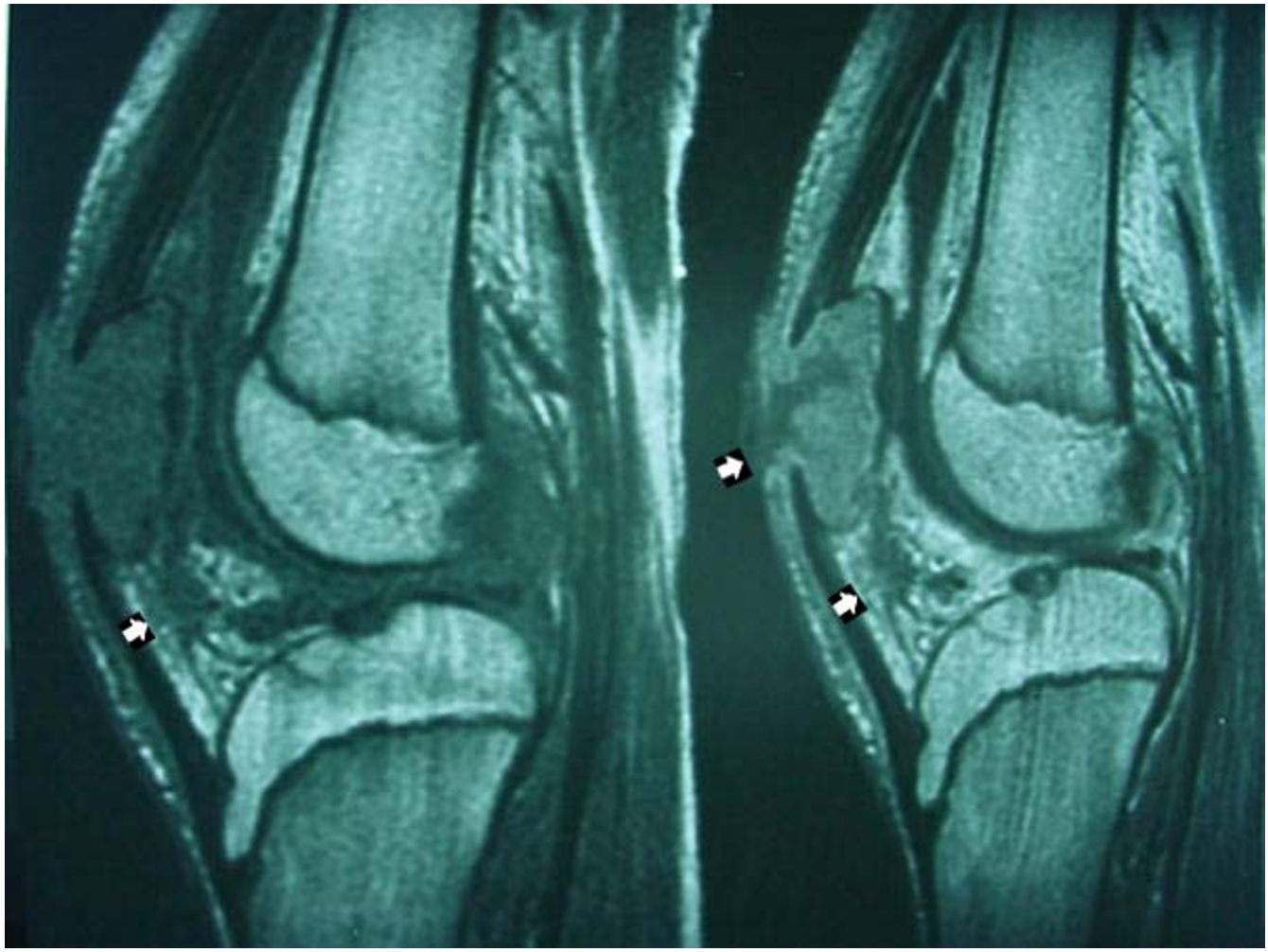

Figure 2
MRI scan showed left knee arthritis, osteomyelitis and fistulated patellar osteomyelitis.

cally excised and another synovial fluid sample was taken from the left knee at the same session. From the tissue samples cultures *Aspergillus fumigatus* were yielded. Antibiotic treatment switched to Amphotericin B deoxicolate 0.7 mg/kg/day. G6PD level were normal. As the nitroblue tetrazolium test (NBT) was positive, the patient was diagnosed as chronic granulomatous disease. Surgical debridement was performed. On the 37 th day at the total dosage of 820 mg of amphotericin B nephrotoxicity developed and the therapy switched to itraconazole 400 mg/day. The infection was treated with surgical debridement and antifungal treatment. At the 37th day, ESR decreased to 25 mm/h and CRP was <5 mg/dl. The surgical wound healing was very slow and we could not introduce IFN-γ because the licensed use of this preparation is not available in our country. The patient was given co-trimoxazole for prophylaxis and itraconazole therapy. As the surgical wound healed, the co-trimoxazole prophylaxis and itraconazole therapy were discontinued at the 6th month. The limitation of the range of motion of the knee joint excellently responded to physical therapy and rehabilitation program that lasted three weeks and a knee joint flexion of 90 degrees was achieved. The patient can perform all the activities of daily living including the school activities and he is not receiving any prophylactic medicine.

Discussion

Arthritis due to aspergillosis is a very rare condition. It can result from the hematogeneous spread from the lungs to the joints and it usually occurs in the setting of an immunocompromised host. Predisposing conditions have been described in the literature, such as chronic granulomatous

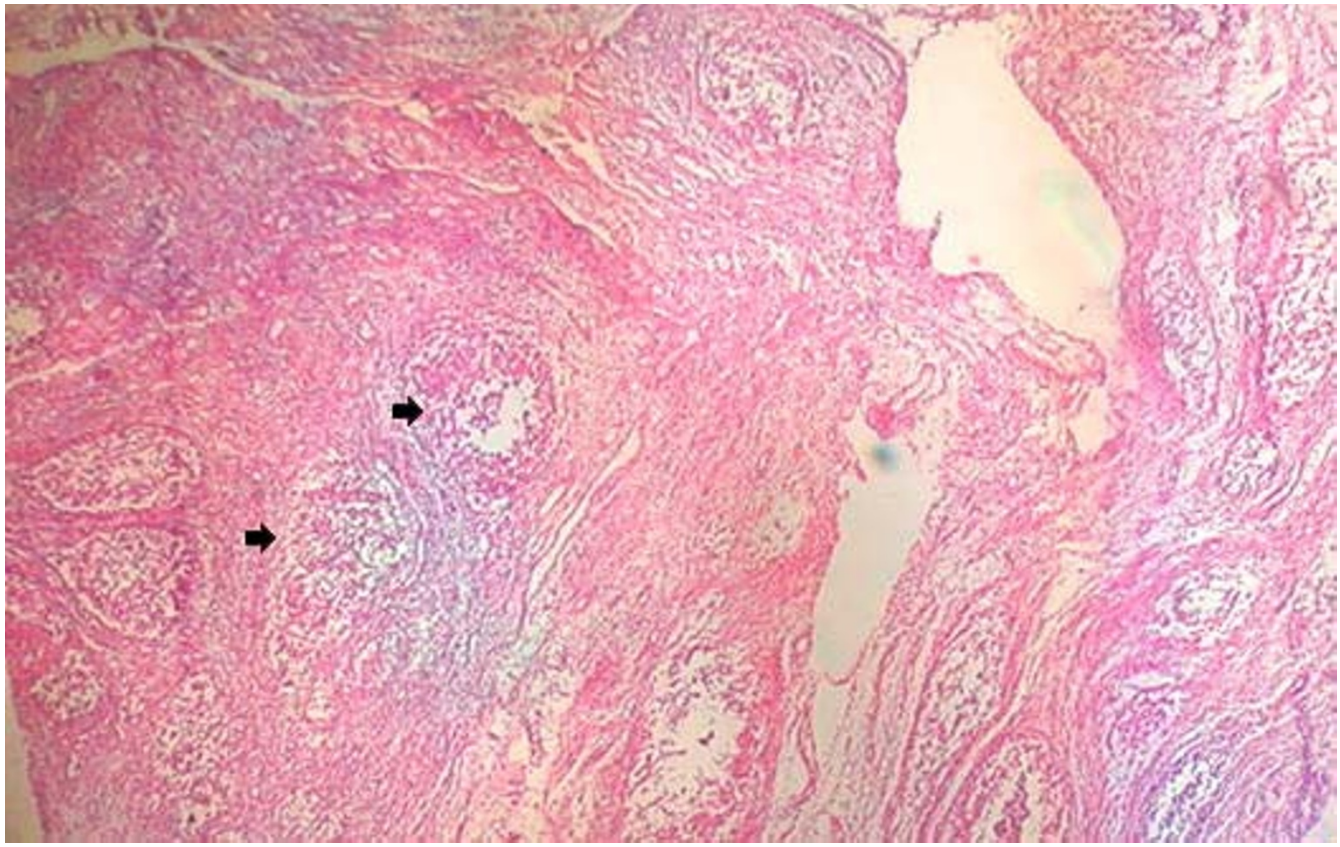

Figure 3
The synovial biopsy of the left knee expressed granulomatous lession due to *Aspergillus*.

disease, corticosteroid therapy, post-renal transplantation and idiopathic thrombocytopenic purpura. However, in immunocompetent patients, *Aspergillus* infection causing arthritis or osteomyelitis usually occurs as an iatrogenic infection after surgery [6]. Our patient did not have any history of trauma or surgical intervention. Moreover, lack of known any immune deficiency state or previous immunosuppressive therapy makes us to think that CGD might be predisposing factor.

Cohen et al. reviewed the records of 245 patients with CGD and found that 20% had a history of fungal infection and *Aspergillus* accounted for 78% of the fungal infections. Invasive *Aspergillus* infection in patients with CGD is associated with mortality rates approaching to 50% [7]. Liese et al evaluated the records of 39 patients with CGD and they stated that infections with *Aspergillus* species have become the major cause of infectious complications and death and among the pneumonia episodes besides *Candida species* and *Pseudomonas aeruginosa, Aspergillus species* were the most frequently isolated microorganisms in patients with CGD [8].

CGD is an 70% X-linked recessive disorder of phagocyte function, in which the phagocytes were unable to generate super oxide anions and other microbicidal oxygen metabolites, resulting in increased susceptibility to infection with a wide variety of bacterial and fungal pathogens [3,5,9,10]. These patients have an inherited phagocyte-killing defect that occurs as a result of biochemical abnormalities in the NADHP oxidase system [9,10].

The most characteristic pathogens are catalase-positive microorganisms or microorganisms that can not generate hydrogen peroxide. Catalase negative organisms such as *Streptococci* are normally killed by the phagositic cells of the patients but microorganisms such as *S. aureus, S. epidermitis, E. coli, S. marcescens, Klebsiella, Pseudomonas, B. cepecia, Proteus, Salmonella, C. albicans* can not be eliminated. Localized and disseminated *M. tuberculosis* and *Aspergillus* infections were also commonly seen [2,5,9,10].

Infections may be acute, subacute or chronic. Besides the delay of tissue healing, acute and chronic inflammatory response may be slow and there may be also a granuloma formation [2,4]. CGD is commonly associated with dermatitis, lymphadenitis, enlargement of liver, spleen and growth retardation [2,3]. The physical examination of our patient also revealed hepatosplenomegaly, axillar multiple lymphadenopathy and retardation of normal growth and development.

These phagocytes unlike normal phagocytes, fail to reduce the histochemical dye nitroblue tetrazolium (NBT) to a blue-black deposit after stimulation with endo-toxin or phorbol myristate acetate. Definite diagnosis can be established by the NBT test [2,5,11] which was also positive in our patient. The normal G6PD levels in our patient make us to think that this is not the autosomal recessive form of this disease. Although the diagnosis of CGD is established at 17 years of age, active Tbc infection when he was 9 years old and a craniotomy operation (probably because of granuloma) and retardation of growth and development shows that our patient has a mild form of CGD for a long time. As we could not reach the biopsy specimen records of the craniotomy operation of the patient when he was three years old, we can not say anything about the nature of the tissue, whether it was due to aspergillus or not. In addition, diagnosis and specific therapy of Tbc were performed in an Education and Research hospital specially dealing with Tbc patients and at this point, we feel confident about the diagnosis of our patient.

Treatment of the arthritis due to *Aspergillus* infection especially needs surgical drainage. The main difference of these lesions was commonly encountered granulomatous masses. A surgical incision and drainage was performed to our patient's knee joint and the obtained synovial tissue biopsy specimen consisted of granulomatous tissue. Only two antifungal agents which have activity against *Aspergillus* are licensed-amphotericin B and itraconazole [12]. For the treatment of *Aspergillus* osteomyelitis, early surgical debridement and amphotericin B is recommended. However, because of the risk of nephrotoxicity the maximum dosage should be 3 grams and the maximum duration of therapy should be 12 weeks [6]. Oral or intravenous itraconazole is a safe and well tolerated agent for the treatment of invasive *Aspergillosis* [13]. In one case report, itraconazole was used for one year after surgical debriment of the osteomyelitis and resulted clinical recovery [14]. Tsumura et al. reported that the initial treatment consisting of surgical debridement and antibiotic therapy with amphotericin B, itraconazole and flucytosine did not control the infection but after administering recombinant IFN-γ it was found to be effective in controlling the course of severe invasive Aspergillosis [15]. For the treatment of *Aspergillus* arthritis, Steinfeld et al. performed an arthroscopic debridement and administered intravenous amphotericin B (60 mg iv every 48 hours) over a 6 week period and oral itraconazole (600 mg daily) for 9 months. The follow-up of the patient revealed very good results without evidence of recurrence [16].

We could not find any report about the caspofungin therapy in CGD in the English literature but we observed three reports about the voriconazole, a large spectrum new triazol, therapy in CGD. van't Hek et al successfully treated a 5 years old patient with CGD and *Aspergillus nidulans* pneumonia with voriconazole in 10 weeks, which did not respond to amphotericin therapy of 6 weeks [17]. Sevaux et al observed clinical response at the second and radiological response at the third month in an adult patient with CGD and *Aspergillus fumigatus* pneumonia with voriconazole therapy [18]. In another study, treatment of 13 CGD children with voriconazole an initial dose 6 mg/kg for the first day and then 4 mg/kg two times daily had a success rate of 62% [19].

Conclusion

Without trauma or surgical intervention, arthritis and osteomyelitis due to *Aspergillus* cannot occur in healthy individuals. Encountering this situation must remind us an immune system defect and the most common predisposing factor for this defect is the CGD in otherwise normal children, which should be searched.

Authors' contributions

HB conceived of the study, and participated in its design and coordination. AC conceived of the study, and participated in observation and treatment of the case. KO carried out the physical therapy and rehabilitation program. YC was performed surgical procedures. NB carried out the microbiological studies. SK carried out the pathological studies.

All authors read and approved the final manuscript.

Acknowledgment

Written consent was obtained from the patient or their relative for publication of the patient's details.

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