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Osteomyelitis due to *Aspergillus* spp. in patients with chronic granulomatous disease: comparison of *Aspergillus nidulans* and *Aspergillus fumigatus*

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Summary *Objective:* Chronic granulomatous disease (CGD) is a rare inherited disorder of NADPH oxidase in which phagocytes fail to generate reactive antimicrobial oxidants. Invasive fungal infections are an important cause of morbidity and mortality in CGD patients, with *Aspergillus* spp. being the most frequent fungal pathogens. We reviewed the reported cases of osteomyelitis in CGD patients due to *Aspergillus nidulans* and compared them with those due to *Aspergillus fumigatus*.

Methods: Twenty-four cases of osteomyelitis due to *Aspergillus* spp. in 22 male CGD patients were found in MEDLINE.

Results: Fourteen cases (58%) were due to *Aspergillus nidulans* and ten cases to *Aspergillus fumigatus*. No other aspergilli were reported as causes of osteomyelitis. Osteomyelitis due to *Aspergillus nidulans* was associated with pulmonary infection and involved 'small bones' more frequently than *Aspergillus fumigatus* osteomyelitis ($p = 0.032$). Half of the CGD patients with *Aspergillus nidulans* osteomyelitis died compared with none of those with *Aspergillus fumigatus* osteomyelitis ($p = 0.019$). In both *Aspergillus nidulans* and *Aspergillus fumigatus* cases, cure was achieved by prompt antifungal treatment combined with surgery and immunotherapy.

Conclusion: *Aspergillus nidulans* causes osteomyelitis in CGD patients relatively frequently compared with *Aspergillus fumigatus* and may be accompanied by higher mortality. This contrasts with the low frequency with which *Aspergillus nidulans* causes osteomyelitis in patients with other types of immunodeficiency.

Introduction

Chronic granulomatous disease (CGD) is a genetically determined primary immunodeficiency disorder in which phagocytic cells are unable to destroy certain bacteria and fungi.[1] The underlying defect is an inability of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex of phagocytes to generate reactive oxidants such as superoxide anion, hydrogen peroxide and hydroxyl radicals, which are key elements in host defence against pathogens.[2] The most common form of the disease is due to an X-linked recessive defect in glycoprotein 91^{phox} ($gp91^{phox}$). The other three

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forms are due to autosomal recessive defects in other major components of the oxidase, p22-phox deficient ($p22^{phox}$), p47-phox deficient ($p47^{phox}$) and p67-phox deficient ($p67^{phox}$), each of which is encoded on a different chromosome.[2]

Chronic granulomatous disease patients are vulnerable to organisms that are catalase positive and thus destroy hydrogen peroxide. These organisms include *Staphylococcus* spp., *Serratia*, *Nocardia*, mycobacteria and *Aspergillus* spp.; *Penicillium*, *Paecilomyces*, *Acremonium*, *Rhizopus* spp. and dematiaceous moulds are isolated less frequently.[3] The lungs are the most common sites of infection. In the US Registry of CGD patients, the majority of them suffered from at least one episode of pneumonia followed by subcutaneous or liver abscesses, suppurative adenitis, osteomyelitis, bacteremia/fungemia, cellulitis and meningitis.[4]

Fungal osteomyelitis due to *Aspergillus* spp. is infrequent in CGD patients. In particular, long bone osteomyelitis due to *Aspergillus* spp. has been rarely described.[5] We recently treated a 16-year-old boy with CGD suffering from femoral osteomyelitis due to *Aspergillus nidulans* without pulmonary involvement, who had a favorable outcome.[6] From this case we proceeded to review all the cases of osteomyelitis due to *A. nidulans* in CGD patients recorded in the English literature (MEDLINE) and to compare them with those due to *Aspergillus fumigatus*.

Literature review and methods

The MEDLINE database was searched using the keywords 'osteomyelitis', 'chronic granulomatous disease' and '*Aspergillus*'. All the articles found by this means were reviewed and a master Excel database was constructed. The references cited in the above articles were screened for additional cases of osteomyelitis due to *Aspergillus* spp. in CGD patients.

A definite diagnosis of *Aspergillus* osteomyelitis required a positive culture of bone tissue obtained by an invasive procedure such as needle aspiration or biopsy. Infection of the chest wall was defined as extensive damage to both thoracic soft tissue and ribs. A debridement was defined as a 'limited' intralesional procedure if no special efforts had been undertaken preoperatively or at operation to define the maximum extent of the lesion and if the debridement had been performed through a limited cortical window. The debridement was considered an 'extensive' intralesional procedure if an attempt had been undertaken to identify the full extent of infection, preoperatively with three-dimensional imaging and at operation with wide exposure, and if all of the involved tissue was debrided until normal tissue was reached.[6]

The statistical program GraphPad Instat (Graphpad Inc., San Diego, CA) was used to compare the cases due to *A. nidulans* with those due to *A. fumigatus*. Statistical evaluation of differences in proportions and calculation of odds ratio (OR) and 95% confidence interval (CI) were performed by Fisher's exact test. A two-sided *P* value of <0.05 indicated statistical significance.

Results

Twenty-four cases of osteomyelitis due to A. *nidulans* and *A. fumigatus* in CGD patients have been recorded in the MEDLINE database to date. Fourteen cases were due to *A. nidulans* (58%) and ten due to *A. fumigatus*. One patient had two bone infections due to *A. nidulans* and another patient had two bone infections due to *A. fumigatus*. In total, 13 patients with CGD suffered from osteomyelitis due to A. *nidulans* (Table 1) and nine due to *A. fumigatus* (Table 2).

Demographics

The median age of the patients when the first episode of *A. nidulans* skeletal infection occurred was 11 years ranging from four to 20 years. Similarly, in cases of osteomyelitis due to *A. fumigatus*, the median age at which the first skeletal infection was identified was ten years ranging from four to 19 years.

All CGD patients with osteomyelitis due to these fungi were male. In all nine patients who suffered from osteomyelitis due to A. *nidulans* whose genetic pattern was reported, it was X-linked inheritance. On the other hand, among three patients suffering from osteomyelitis due to *A. fumigatus* whose genetic pattern was reported, it was X-linked $gp91^{phox}$ in two and autosomal recessive form $p67^{phox}$ in one (Table 3).

Sites of infection

The most frequently affected bones in cases of osteomyelitis due to *A. nidulans* in CGD patients were vertebrae, followed by ribs and other chest wall bones and soft tissue (Table 4). In 12 of the 14 cases (86%), osteomyelitis of small bones resulted from contiguous spread of pulmonary infection; only in two of the 14 cases (14%), lungs were not involved.

Table 1 Cases of osteomyelitis due to *Aspergillus nidulans* in patients with chronic granulomatous disease, sorted by year of diagnosis.

Patient[a]	Reference	Age (yr)	Genotype[b]	Year of publication	Site	Antifungal therapy	Adjunctive therapy	Surgery	Outcome
1	7	6	NA	1965	Ribs, vertebrae[c]	DAMB	No	Yes	Died
2	8	8	gp91^{phox}	1974	Rib[c]	DAMB	WBC transfusion	No	Survived
3	9	10	NA	1977	Ribs, vertebrae[c]	DAMB	No	Yes	Survived
4	3	4	gp91^{phox}	1998 (diagnosis in 1986)	Chest wall, vertebrae[c]	DAMB + flucytosine	IFN-γ + WBC transfusion	Yes	Died
5	10	20	gp91^{phox}	1989	Rib, femur, skull[c]	DAMB + flucytosine + itraconazole	No	Yes	Survived
6	5	4	X-linked	1991	Ribs, vertebrae[c]	DAMB	WBC transfusion	Extensive	Died
7	5	9	gp91^{phox}	1991	Rib[c]	DAMB	No	Yes	Survived
7	5	13	gp91^{phox}	1991	Vertebrae[d]	DAMB	No	Extensive	Survived
8	3	19	gp91^{phox}	1998 (diagnosis in 1992)	Chest wall, vertebrae, skull[c]	DAMB + LAMB + flucytosine	IFN-γ + WBC transfusion + local instillation of granulocytes and hydrogen peroxide	Yes	Died
9	3	16	gp91^{phox}	1998 (diagnosis in 1993)	Chest wall, vertebrae[c]	DAMB + LAMB + itraconazole	IFN-γ + WBC transfusion	Yes	Survived
10	11	19	gp91^{phox}	1994	Chest wall[c]	DAMB + LAMB + itraconazole + fluconazole + rifampicin + flucytosine	G-CSF + WBC transfusion	No	Died
11	3	7	gp91^{phox}	1998 (diagnosis in 1996)	Chest wall, vertebrae[c]	DAMB + LAMB + flucytosine	IFN-γ + WBC transfusion	Yes	Died
12	12	6	NA	1997	Chest wall, vertebrae[c]	DAMB + itraconazole	GM-CSF + IFN-α	Yes	Died
13	6	16	NA	2003	Left femur[d]	LAMB + itraconazole	IFN-γ + local instillation of DAMB + G-CSF	Extensive	Survived

NA: not available; gp91^{phox}: glycoprotein 91^{phox}; DAMB: deoxycholate amphotericin B; LAMB: liposomal amphotericin B; ABLC: amphotericin B lipid complex; WBC: white blood cells; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte-macrophage colony stimulating factor; IFN-α: interferon-α; IFN-γ: interferon-γ.

[a] All patients were male.

[b] gp91^{phox} is the X-linked gene that encodes the 91Kd transmembrane protein of the NADPH oxidase complex, p67^{phox} encodes the 67Kd cytosolic subunit of the NADPH oxidase complex.

[c] Contiguous spread from a pulmonary infection.

[d] Bone infection without pulmonary infection.

Table 2 Cases of osteomyelitis due to *Aspergillus fumigatus* in patients with chronic granulomatous disease, sorted by year of diagnosis.

Patient[a]	Reference	Age (yr)	Genotype[b]	Year of publication	Site	Antifungal therapy	Adjunctive therapy	Surgery	Outcome
1	13	6	NA	1983	Primary in left femur, secondary in vertebrae[d]	DAMB + flucytosine	No	Limited	Survived
2	14	4	NA	1987	Cranium[d]	DAMB + flucytosine	No	Extensive	Survived
3	15	18	NA	1990	Ribs and left humerus[c]	DAMB → itraconazole	No	No	Survived
4	5	19	gp91^{phox}	1991	Sternum[c]	DAMB	WBC transfusion	Extensive	Survived
5	16	15	NA	1991	Right humerus[d]	DAMB + flucytosine → itraconazole p.o.	IFN-γ	Extensive	Survived
6	17	10	NA	1994	Right second rib[c]	Itraconazole	IFN-γ	No	Survived
6	17	11	NA	1994	1st, 2nd and 3rd thoracic vertebrae[d]	DAMB + itraconazole → ABLC + itraconazole	IFN-γ + WBC transfusion	No	Survived
7	3	7	gp91^{phox}	1998 (diagnosis in 1995)	Chest wall[d]	DAMB	No	Extensive	Survived
8	18	10	NA	1996	Right femur[c]	Itraconazole	IFN-γ	No	Survived
9	19	9	p67^{phox}	1999	Tibia[d]	Fluconazole → DAMB−itraconazole p.o.	IFN-γ	Extensive	Survived

NA: not available; gp91^{phox}: glycoprotein 91^{phox}; DAMB: deoxycholate amphotericin B; ABLC: amphotericin B lipid complex; WBC: white blood cells; IFN-γ: interferon-γ.

[a] All patients were male.

[b] gp91^{phox} is the X-linked gene that encodes the 91Kd transmembrane protein of the NADPH oxidase complex, p67^{phox} encodes the 67Kd cytosolic subunit of the NADPH oxidase complex.

[c] Contiguous spread from a pulmonary infection.

[d] Bone infection without pulmonary infection.

Table 3 Relationship between genetic subtypes of chronic granulomatous disease and osteomyelitis due to *Aspergillus* spp.

Genetic subtype	*Aspergillus nidulans* (13 patients)	*Aspergillus fumigatus* (9 patients)	Total (22 patients)
X linked CGD[a]	9 (8)	2 (2)	11
$p67^{phox}$-deficient	None	1	1
Not reported	4	6	10

[a] $gp91^{phox}$-deficient pattern in parenthesis.

Two cases[3,10] exhibited multifocal extension; in one of them the affected bones were chest wall, vertebrae and skull.[3] Only two cases of femoral osteomyelitis due to *A. nidulans* were described.[6,10] In the first case,[10] osteomyelitis was part of a multifocal disseminated disease also involving the lungs (probably the portal of entry) ribs, skull and femur. To our knowledge, the second case[6] was the only case of *A. nidulans* long-bone osteomyelitis described in a CGD patient without simultaneous pulmonary infection.

By comparison, osteomyelitis due to *A. fumigatus* showed no predilection for particular bones (Table 4). Two multifocal osteomyelitis cases were described.[13,15] The bones most frequently involved were ribs, vertebrae, humerus and femur. In four of the ten published cases (40%), the bone infection was probably the result of contiguous spread of pulmonary infection. In the remaining six cases, the lungs were not involved. Osteomyelitis due to *A. nidulans* was more frequently associated with pulmonary infection (12 out of 14—86% of cases) than that due to *A. fumigatus* (four out of ten—40% of cases; OR = 9.0, 95% CI 1.27 to 63.9, $p = 0.032$).

Table 4 Site of osteomyelitis in cases due to *Aspergillus nidulans* or *Aspergillus fumigatus* in patients with chronic granulomatous disease.

Site	*Aspergillus nidulans* ($n = 14$) (%)	*Aspergillus fumigatus* ($n = 10$) (%)
Vertebrae	9 (64)	2 (20)
Ribs	6 (43)	2 (20)
Chest wall	6 (43)	1 (10)
Femur	2 (14)	2 (20)
Humerus	0	2 (20)
Skull	2 (14)	1 (10)
Tibia	0	1 (10)
Sternum	0	1 (10)

Antifungal therapy

Amphotericin B was used in 22 of the 24 (92%) cases of *Aspergillus* osteomyelitis (Table 5). In all the cases of osteomyelitis due to *A. nidulans*, amphotericin B was used as drug of first choice. In five of 14 cases (36%), the liposomal form of the drug was used. For the treatment of *A. fumigatus* osteomyelitis, amphotericin B was used in eight of ten cases (80%), and amphotericin B lipid complex was utilized in only one case. In two cases of *A. fumigatus* osteomyelitis, monotherapy with itraconazole resulted in a favorable response. Flucytosine was always used together with amphotericin B. In one case, rifampicin was used together with amphotericin B, itraconazole, flucytosine and fluconazole[11] and in another case local instillation of deoxycholate amphotericin B was utilized.[6]

Immunotherapy

White blood cell (WBC) transfusions have been suggested for the control of major infections in patients with CGD.[20] From a total of 24 cases, WBC transfusions were administered in nine (38%) of them (Table 5). In particular, WBC transfusions were administered in seven of 14 cases (50%) of *A. nidulans* bone infections and in two of ten cases (20%) of *A. fumigatus* bone infections ($p = 0.21$). The WBC transfusions were given three to five times each week for up to three weeks. Interferon-γ (IFN-γ) was also used in ten of 24 (42%) cases with no difference between *A. nidulans* and *A. fumigatus* cases. Although the numbers of patients were small, there was no significant difference in survival rate between IFN-γ-treated and non-treated patients with *A. nidulans* osteomyelitis.

In only three of 14 (21%) cases of *A. nidulans* and in no case of *A. fumigatus* osteomyelitis, granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) were used. In persistent cases, other

Table 5 Antifungal drug treatment and immunotherapy of osteomyelitis cases due to *Aspergillus nidulans* and *Aspergillus fumigatus* in patients with chronic granulomatous disease.

Treatment	*Aspergillus nidulans* ($n = 14$)	*Aspergillus fumigatus* ($n = 10$)
Amphotericin B	14	8
Deoxycholate amphotericin B	13	8
Liposomal amphotericin B	5	0
Lipid complex amphotericin B	0	1
Itraconazole	5	6
Flucytosine	5	3
Fluconazole	1	1
Rifampicin	1	0
Interferon-γ	5	5
Interferon-α	1	0
Transfusion of white blood cells	7	2
Granulocyte colony stimulating factor	2	0
Granulocyte-macrophage colony stimulating factor	1	0
Local instillation of deoxycholate amphotericin B	1	0
Local instillation of granulocytes and hydrogen peroxide	1	0

Table 6 Relationship between surgery and mortality in cases of osteomyelitis due to *Aspergillus nidulans* and *Aspergillus fumigatus* in patients with chronic granulomatous disease.

	Aspergillus nidulans	*Aspergillus fumigatus*	*P* value
Number of cases	14	10	
Mortality	7 (50%)	0 (0%)	0.019
Number of cases with surgery	12	6	
Mortality with surgery	6 (50%)	0 (0%)	0.054
Number of cases without surgery	2	4	
Mortality without surgery	1 (50%)	0 (0%)	

adjunctive therapies such as interferon-α (IFN-α) or local instillation of granulocytes and hydrogen peroxide were used with varying results.

Surgery

Surgical debridement appears to have played a very important role in the treatment of osteomyelitis due to *Aspergillus* spp. In 18 of 24 cases (75%), surgical debridement combined with antifungal agents was used (Table 6). In the remaining six cases (25%), treatment was attempted with antifungal agents alone, but in one of the two cases of *A. nidulans* infection it resulted in death. Because some of the infections involved several compartments, a true wide margin was usually impossible and was obtained for only one infection. A limited intralesional debridement appeared to be less effective than extensive debridement especially in osteomyelitis cases due to *A. nidulans*.[3,5]

Outcome

The overall mortality of osteomyelitis in CGD patients was seven deaths in 24 cases (29%). However, the mortality among patients with osteomyelitis due to *A. nidulans* was 50% (seven deaths in 14 cases). By contrast, in patients with osteomyelitis due to *A. fumigatus* there were no reported deaths (no deaths in ten cases; OR = 21.0, 95% CI = 1.03 to 427.3, $p = 0.019$). This difference in mortality between *A. nidulans* and *A. fumigatus* cases tended to be observed even after surgical therapy (OR = 13.0, 95% CI 0.6 to 281.7, $p = 0.054$; Table 6).

Discussion

This review of the reported cases of osteomyelitis due to *Aspergillus* spp. in CGD patients suggests that:

1. *A. nidulans* causes osteomyelitis in these patients more frequently than *A. fumigatus*.
2. *A. nidulans* may affect 'small bones' in connection with lungs more frequently than *A. fumigatus* does.
3. *A. nidulans* is associated with increased mortality compared with *A. fumigatus*.

Taking into account that this is a retrospective, multi-source case review study, limitations imposed by the data may affect the strength of conclusions drawn from it.

A. fumigatus is by far the most common filamentous fungus, causing 80—90% of cases of invasive aspergillosis in immunocompromised patients[21] and is the most frequent cause of invasive aspergillosis in CGD patients.[4] However, *A. nidulans* was found to be a more frequent cause of osteomyelitis in CGD patients than *A. fumigatus*. Why this particular association of *A. nidulans* with skeletal infections exists in CGD patients is unclear. What is clear, however, is that *A. nidulans* osteomyelitis in CGD patients is frequently associated with pulmonary aspergillosis and with increased mortality compared with *A. fumigatus* osteomyelitis.

Historically, the overall incidence of fungal infections has been reported to be 20% in CGD patients, with *Aspergillus* spp. being responsible for 78% of all fungal infections in these patients.[22] More recently, *Aspergillus* spp., especially *A. fumigatus*, have become one of the predominant causes of infections in CGD patients.[4] Aspergillosis is the most common cause of mortality in patients with CGD and is responsible for over one third of deaths. Osteomyelitis in CGD patients, most frequently resulting from contiguous spread of a pulmonary infection, has occurred in 25% of patients. *Aspergillus* spp. are the second most common cause, accounting for approximately 22% of all osteomyelitis cases.[4]

The most serious pattern of infectious involvement in CGD patients was the spread of infection from an abscess in the lung to the bones of the thoracic wall and spine. Complete debridement of the site of vertebral infection is extremely difficult anatomically, although the procedure can be successful.[5] Thus, the earlier a vertebral infection is debrided, the more complete the debridement can be and in cases in which it was performed, the patients had an excellent response.

Patients with the X-linked recessive form of the disease appear to have a more serious clinical phenotype than patients with the autosomal recessive forms of the disease, based on the fact that they are diagnosed significantly earlier in the course of the disease and they have a significantly higher prevalence of infections.[3] In the 11 cases where the patient had the X-linked recessive form (including $gp91^{phox}$-deficiency) of the disorder, a mortality of 45.5% (five of 11 cases) was observed.

Patients with *A. nidulans* osteomyelitis received longer courses of amphotericin B therapy than patients with *A. fumigatus* osteomyelitis.[3] Because the literature on osteomyelitis due to the two *Aspergillus* spp. in patients with CGD is limited to case reports in which disparate therapies were provided, it is difficult to define the best treatment of this devastating infection.[3] Nevertheless, in *A. nidulans* osteomyelitis early extensive surgery appears to be important.

Hematopoietic growth factors may play an important role in the treatment of invasive aspergillosis in patients with CGD.[23] The use of hematopoietic factors and T helper 1 cytokines in aspergillosis[6,12,16—19] seems to be effective. G-CSF acts on polymorphonuclear leukocytes (PMNs), promoting their maturation and increasing their number in peripheral blood, helping patients to clear infections such as osteomyelitis due to *A. nidulans*. On the other hand, GM-CSF may be more helpful as it acts on both granulocytic and monocytic lineages, regulating not only the number of PMNs but also of macrophages. The use of IFN-γ in patients with CGD as prevention and therapy may also be helpful.[24] In parallel with the use of antifungal agents, improving immune response by either exogenous modulation of enhancing/regulatory cytokines or by transfusion of cytokine-elicited allogeneic phagocytes appears to be a promising adjunct to antifungal chemotherapy.

Conclusion

In conclusion, this study shows that osteomyelitis due to *A. nidulans* may be more common in CGD patients and more difficult to control than that due to *A. fumigatus*. Osteomyelitis due to *A. nidulans* causes increased morbidity and mortality in CGD patients and requires prompt medical and surgical treatment.

Conflict of interest: No conflicting interest declared.

References

1. Segal BH, Leto T, Gallin JI, Malech HL, Holland SM. Genetic, biochemical and clinical features of chronic granulomatous disease. *Medicine* 2000;**79**:170—200.
2. Segal AW. The NADPH and chronic granulomatous disease. *Mol Med Today* 1996;**2**:129—35.

3. Segal BH, De Carlo ES, Kwon-Chung KJ, Malech HL, Gallin JI, Holland SM. *Aspergillus nidulans* infection in chronic granulomatous disease. *Medicine* 1998;**77**:1659—65.
4. Winkelstein JA, Marino MC, Johnston RB, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine* 2000;**79**:155—69.
5. Sponseller PD, Malech HL, McCarthy Jr EF, Horowitz SF, Jaffe G, Gallin JI. Skeletal involvement in children who have chronic granulomatous disease. *J Bone Joint Surg Am* 1991;**73**:37—51.
6. Dotis J, Panagopoulou P, Winn R, Toptsis C, Panteliadis C, Roilides E. Femoral osteomyelitis due to *Aspergillus nidulans* in a patient with chronic granulomatous disease. *Infection* 2003;**31**:121—4.
7. Redmond A, Carre IJ, Biggart JD, Mackenzie DWR. Aspergillosis (*Aspergillus nidulans*) involving bone. *J Pathol Bacteriol* 1965;**89**:391—5.
8. Bujak JS, Kwon-Chung KJ, Chusid MJ. Osteomyelitis and pneumonia in a boy with chronic granulomatous disease of childhood caused by a mutant strain of *Aspergillus nidulans*. *Am J Clin Pathol* 1974;**61**:361—7.
9. Altman AR. Thoracic wall invasion secondary to pulmonary aspergillosis: a complication of chronic granulomatous disease. *Am J Roentgenol* 1977;**129**:140—2.
10. Neijens HJ, Frenkel J, de Munick Keizer-Schrama SMPF, Dzoljic-Danilovic G, Meradji M, van Dongen JJM. Invasive *Aspergillus* infection in chronic granulomatous disease: treatment with itraconazole. *J Pediatr* 1989;**115**: 1016—9.
11. Näke A, Kerkmann ML, Blaschke-Hellmessen R, Henker J, Schwarze R. Invasive aspergillosis in a child with chronic granulomatous disease: A try with liposomal bound amphotericin B. *Pädiatr Grenzeb* 1994;**33**:109—15.
12. Kim M, Shin JH, Suh SP, et al. *Aspergillus nidulans* infection in a patient with chronic granulomatous disease. *J Korean Med Sci* 1997;**12**:244—8.
13. de la Cruz R, Jain M, Hsu K, Lim DT. Intrinsic polymorphonuclear chemotactic defect in a boy with chronic granulomatous disease. *Allergol Immunopathol (Madr)* 1983;**11**: 457—64.
14. Pollack IF, Pang D, Schuit KE. Chronic granulomatous disease with cranial fungal osteomyelitis and epidural abscess. *J Neurosurg* 1987;**67**:132—6.
15. van't Wout JW, Raven EJ, van der Meer JW. Treatment of invasive aspergillosis with itraconazole in a patient with chronic granulomatous disease. *J Infect* 1990;**20**:147—50.
16. Heinrich SD, Finney T, Craver R, Yin L, Zembo MM. *Aspergillus* osteomyelitis in patients who have chronic granulomatous disease. *J Bone Joint Surg Am* 1991;**73**:456—60.
17. Kline MW, Bocobo FC, Paul ME, Rosenblatt HM, Shearer WT. Successful medical therapy of *Aspergillus* osteomyelitis of the spine in an 11-year-old boy with chronic granulomatous disease. *Pediatrics* 1994;**93**:830—5.
18. Pasic S, Abinun M, Pistignjat B, et al. *Aspergillus* osteomyelitis in chronic granulomatous disease: treatment with recombinant gamma-interferon and itraconazole. *Pediatr Infect Dis J* 1996;**15**:833—4.
19. Tsumura N, Akasu Y, Yamane H, et al. *Aspergillus* osteomyelitis in a child who has p67-phox-deficient chronic granulomatous disease. *Kurume Med J* 1999;**46**:87—90.
20. Fanconi S, Seger R, Gmür J, et al. Surgery and granulocyte transfusions for life threatening infections in chronic granulomatous disease. *Helvetica Paediatr Acta* 1985;**40**:277—84.
21. Denning DW. Invasive aspergillosis. *Clin Infect Dis* 1998;**26**:781—803.
22. Cohen MS, Isturiz RE, Malech HL, et al. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. *Am J Med* 1981;**71**:59—66.
23. Roilides E, Lamaignere CG, Farmaki E. Cytokines in immunodeficient patients with invasive fungal infections: an emerging therapy. *Int J Infect Dis* 2002;**6**:154—63.
24. The International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. N Engl J Med 1991;**324**:509—16.