# VERTEBRAL ASPERGILLOSIS
# A CASE REPORT AND REVIEW OF THE LITERATURE

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**A case of Aspergillus osteomyelitis of the spine is presented and the world literature is reviewed, for a total of 32 cases. Aspergillus osteomyelitis is rare, but the spine is most frequently affected. It can be induced hematogenously, by contiguity or by direct inoculation. Up to now medical treatment has been based on amphotericin B, but its toxicity is problematic. Itraconazole and fluconazole do not have this shortcoming. Additional surgery has been advocated in the past. In the present series combined medical-surgical treatment (20 cases) led to a higher survival rate (70%) than medical treatment (12 cases : 58%), but neurological recovery was much more frequent in the second group (40% versus 13%).**

**Keywords** : mycosis ; disc space ; infection ; spondylitis ; aspergillosis ; osteomyelitis ; vertebral.
**Mots-clés** : mycose ; espace intervertébral ; infection ; spondylite ; aspergillose ; ostéomyélite ; rachis.

## INTRODUCTION

The genus Aspergillus (3), a fungus first described by Micheli in 1729, is commonly found in water, soil, decaying vegetation, hay, straw, air, grains (wigmakers and pigeon crammers), flour and vegetable matter. It can contaminate ventilation systems. It can also be isolated from the oropharynx and gastrointestinal tract of normal hosts. In other words, it is a saprophytic fungus, seldom pathogenic for normal hosts. About 200 species have been described, but the following are most often pathogenic in man : fumigatus (most common), flavus, niger, terreus and nidulans.

The human body can react to it in three major ways ; the milder forms tend to occur in normal hosts, while the life-threatening forms are well known in immunocompromised patients, but exceptions do exist.

— *Allergic disease*, ranging from asthma to allergic bronchopulmonary aspergillosis, is a relatively benign type of aspergillosis.
— *Superficial and locally invasive* infection is an intermediate type and includes ear infection, cutaneous infection, orbital infection, sinus infection, pulmonary aspergilloma (mostly in preexisting cavities), pleuritis and empyema, urinary tract aspergillosis and peritonitis.
— Major organ and disseminated infection, also called *invasive aspergillosis*, may follow a surgical procedure via direct inoculation, sometimes from a defective ventilation system, or a pulmonary infection may acutely invade the lung and lead to hematogenous dissemination (in adults) or contiguous spread (in children) to the ribs or vertebrae (27). Indeed, the organism can traverse all natural barriers, including cartilage and bone, causing sino-orbital infection, meningitis, brain abscess, or infection of any organ. The extrapulmonary sites most often affected are the brain, heart, kidney and gastrointestinal tract. The portal of entry can be the respiratory tract (most frequently), the gastrointestinal tract, the skin, a wound (operative or not), venous puncture (catheters, drug addicts), a sinus, the orbits, or the ear.

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The major predisposing factors are immunosuppressive conditions (neutropenia above all others, steroid treatment, cancer, organ transplants, chronic hepatitis, alcoholism, diabetes, lupus, burns, chronic granulomatous disease with defective phagocytosis, drug addiction, AIDS), surgical procedures (especially the insertion of prosthetic devices), antibiotic therapy, intravenous catheters, prior infection and trauma. In the compromised host Apergillus is second only to Candida as a cause of systemic mycotic infection (23). Aspergillus osteomyelitis is rare, but the spine is most frequently affected (2). Osteomyelitis can be induced hematogenously, by contiguity, or by direct inoculation.

## CLINICAL PICTURE

Barnwell (2) noted local pain in 66.7% of 27 patients with Aspergillus osteomyelitis, described in the literature. Of these, 63% had vertebral involvement. Only 29.6% were febrile ; leucocytosis was abnormal in 21.4%. The sedimentation rate was increased in 37% : mean 83 mm, range 33 to 135. Radiographs were abnormal in all 26 patients in whom radiographic examination was reported.

## DIAGNOSIS

The disease is becoming more and more frequent, but the diagnosis is still a problem (3). Single or multiple rounded densities on chest radiographs can be indicative. Computed tomography of the lungs may be more sensitive. Culturing Aspergillus from the respiratory tract secretions is difficult, the success rate ranging from 0 to 56%. Even bronchoscopy and bronchoalveolar lavage have not changed this situation. Tissue fragments are more useful than surface swabs. A positive culture in a susceptible patient is highly significant. Histologically the acutely branching, broad, septate hyphae can be demonstrated with Gomori methenamine silver stain. However, even isolation of Aspergillus is sometimes ignored, as it is a frequent airborne contaminant, and even a saprophyte in man. Nonetheless repeated isolation of organisms and histopathological demonstration of hyphae in biopsies, consistent with cultures, plead for aspergillosis.

In the past, trials to develop a serological test were first centered on the detection of antibodies. The results were often disappointing. Detection of the serum Aspergillus antigen however seems to be more promising for evaluation of disease activity, efficiency of treatment and prognosis. Talbot (28) used a radioimmunoassay technique ; he found a sensitivity of 74% and a specificity of 90%. Moreover, antigen serodiagnosis is independent of host humoral reponses, which are often diminished in the imunocompromised patient.

## TREATMENT

Treatment has been based, up to now, on amphotericin B, but with a mortality of 72% in immunocompromised hosts (3). This poor outcome was partially due to the late diagnosis, often post mortem, because cultures and serological tests were so often disappointing. For this reason empiric administration of amphotericin B has been proposed in neutropenic patients with fever unresponsive to antibacterial therapy. The same has been advised for susceptible patients, with an eschar on the nose or palate and other suspect lesions. Of course, the underlying deficiency in host defenses should also be corrected, if possible. The proper dosage of the very toxic amphotericin B is not yet clear. The initial dose is 0.1 to 0.2 mg/kg/day, by slow infusion (dextrose 5% only). If tolerated, this dose is progressively increased with 0.1 mg/kg daily increments, with regular checks of blood area nitrogen and serum creatinine, complete blood count, liver functions and potassium level. A final dose of 1 mg/kg/day is generally accepted and should be continued at least until significant nephrotoxicity occurs (serum creatinine $>$ 3 mg/dl) (3). Resistance to the drug is possible. Some authors (12) claim that a total dose of 500 mg and continuation for more than one week is beneficial, while others see no relation of outcome with total dose (18). Some indicate a total dose of 3 mg (7). Others (27) continue the treatment for 6 to 12 weeks. Some (1) use the drug only every other day. Follow-up treatment is often advised (3). Disadvantages are : nephrotoxicity

and side effects like fever, anorexia, phlebitis and headache. The erythrocyte sedimentation rate reflects the efficiency of the treatment. Rifampin and 5-fluorocytosine are considered to have a synergistic action with amphotericin B and are administered by mouth.

Two new triazoles (1), itraconazole and fluconazole, seem to be promising. Itraconazole has several advantages : oral administration, good tissue absorption (except by the nervous system), and good tolerance. A single postprandial dose of 200 to 400 mg per day is advised ; it must be adapted to the serum level obtaned.

Granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factor can stimulate production of neutrophils. Transfusions of white blood cells have been proposed in patients with chronic granulomatous disease (10, 13).

Prophylaxis is based on the use of HEPA filters in hospital ventilatory systems (3). Copper-8-quinolinolate is effective for previously contaminated air systems. Susceptible patients can take nystatin and ketoconazole orally as prophylaxis. Operative treatment can be used alone or in combination with medical treatment.

## CASE REPORT

A 54-year-old woman (table I, case 5) underwent an L4L5 discectomy in another hospital on April 14, 1988. Five months later, in September 1988, she complained of severe low back pain. An L3L4 discitis one level above the discectomy was diagnosed radiographically. A needle biopsy was performed, but the culture remained negative. A tuberculin test was also negative. Penicillin was administered, first intravenously and later by mouth.

The patient was first seen in the university outpatient clinic on February 10, 1989. She was afebrile. The last sedimentation rate was 50 mm on January 26, 1989. The pain was tolerable. Further bedrest and continuation of antibiotic treatment were advised.

In May 1989 the pain became worse. The radiographs showed spontaneous fusion of the L3L4 disc and recent involvement of the L2L3 disc. All antibiotics were stopped for 2 weeks, and a Craig needle biopsy of the L2L3 disc was performed on June 8, 1989. Aspergillus fumigatus was cultured from the specimen. PAS alpha and Grocot stains of the specimen also showed a few hyphae, but accidental contamination could not be excluded, according to the pathologist. Penicillin was continued.

However, the pain increased, and the sedimentation rate rose to 92 mm on July 18, 1989 ; the white blood cell count to 12,700 per $mm^3$. On July 27, 1989, the L2L3 disc was curetted via a left iliolumbar approach, and was found to have a gelatinous aspect. It was fused with rib grafts. Microscopic examination of the specimen was negative, but Aspergillus fumigatus was cultured again, and the diagnosis of aspergillosis was finally made. Itraconazole was started at an oral dose of 100 mg twice daily. The pain soon abated. A precipitin test showed 5 lines on August 3, 1989, and 10 lines on August 21, 1989. Postoperatively, extension of the infection to the L1L2 disc was established radiographically. Bedrest was continued until 3 months after curettage.

The treatment with itraconazole was continued for 11 months. In June 1990 the sedimentation rate was 18/47 mm, and the L1L2, L2L3 and L3L4 discs were found to be completely fused.

Granulocyte function was impaired ; lymphocyte stimulation was normal. Very probably the infection occurred at the original operation. At follow-up in June 1992 complete healing was established.

## REVIEW OF THE LITERATURE

In 1982 Tack (27) compiled 19 cases of Aspergillus osteomyelitis, 12 of which concerned the vertebrae. The present study led to a total of 32 vertebral cases, including a single personal case (table I). There were 8 women and 23 men ; in one case the sex was not reported. The average age was 38 years, range 6 months to 73 years. Diminished immunity was present in 21 cases, or 66%. The following species were responsible : fumigatus in 19 cases or 59%, flavus in 4 cases or 13%, nidulans in 3 cases or 9%, terreus in 2 cases or 6%, fumigatus/nidulans in one case or

Table I. — Outcome as a function of treatment

| Case n° Reference Sex Age | Diminished immunity | Strain | Spread | Level | Clinical picture | Antibiotics | Spinal surgery | Outcome |
|---|---|---|---|---|---|---|---|---|
| A. Mixed medical-surgical treatment | | | | | | | | |
| 1 (1) M 20 y | + | Fumig. | Hematog. | L1L2 | Radicular pain | Amph. B Itraconazole 5-fluoro | + | Healed |
| 2 (2) M 38 y | + | Fumig. | Contig. (lung) | T4 | Paraplegia | Amph. B 5-fluoro | + | Healed but paraplegic |
| 3 (6) F 32 y | + | ? | ? (renal transpl.) | L4L5 | Paraparesis | Amph. B | + | Died |
| 4 (7) M 64 y | + | Fumig. | Hematog. (lung) | T11T12 | Back pain | Sulfamethoxazole Antitubercular drugs | + | Healed |
| 5 described here F 54 y | + | Fumig. | Direct (discectomy) | L1L2L3L4 | Low back pain | Itraconazole | + | Healed |
| 6 (9) M 20 y | — | Fumig. | Contig. (lung) | T1T2T3 | Parapleg. | Amph. B | + | Healed, but paraplegic |
| 7 (16) M 44 y | ± | Flavus | Direct (discectomy) | L5S1 | Paresis L5S1 | Amph. B 5-fluoro | + | Healed |
| 8 (16) M 57 y | — | Flavus | Direct (discectomy) | L3L4 | Back pain | Amph. B | + | Healed |
| 9 (16) F 61 y | + | Fumig. | Direct (splenectomy) | L5S1 | L5 sciatica | Amph. B 5-fluoro | + | Died |
| 10 (17) M 22 y | — | Fumig. | Hematog. (lung ?) | T10T11T12 | Paraplegia | Amph. B Rifampicin | + | Healed, but paralytic |
| 11 (19) M 61 y | ± | Fumig. | Hematog. (lung) | T3T4 | Back pain | Amph. B 5-fluoro Rifampicin | + | Healed |
| 12 (23) F 42 y | ++ | Terreus | Hematog. (drug user) | L1L2 | Back pain | Amph. B | + | Healed |

| Case n° Reference Sex Age | Diminished immunity | Strain | Spread | Level | Clinical picture | Antibiotics | Spinal surgery | Outcome |
|---|---|---|---|---|---|---|---|---|
| 13 (24) F 62 y | — | Fumig. | Contig. (lung) | T2 | Paresis right leg | Amph. B | + | Healed but paraplegic |
| 14 (26) M 4 y | + | Nidul. | Contig. (lung) | T8T9T10 | Paraparesis | Amph. B Interferon White blood cells | + | Died paraparetic |
| 15 (26) M 13 y | + | Nidul. | Contig. (lung) | T3T4 | Paraparesis | Amph. B | + | probably healed, died at age 18 of unrelated pulmonary infection |
| 16 (27) F 61 y | + | Fumig. | Hematog. | L5 | Back pain | Amph. B | + | Died of septicemia with Staph. epid. |
| 17 (27) M 45 y | ± | Fumig. | Direct | L5 | Back pain | Amph. B | + | Healed |
| 18 (27) M 58 y | — | Flavus | Direct | L3L4 | Back pain | Amph. B | + | Healed |
| 19 (29) M 6 y | — | ? | Contig. (lung) | T3T4 | Local swelling | Aureomycin Chloromycetin | ± | Died |
| 20 (30) M 53 y | + | Fumig. | Contig. (lung) | T4 | Paraplegia | Amph. B | + | Died |
| B. Medical treatment only | | | | | | | | |
| 21 (4) M 73 y | — | Fumig. | Contig. (aortic bypass) | L2L3 | Back pain | Amph. B | — | Healed |
| 22 (8) F 72 y | + | Fumig. | Hematog. (lung) | L3L4 | Back pain | Amph. B 5-fluoro Itraconazole | — | Healed |
| 23 (11) M 5 y | + | Fumig. + Niger | Contig. (lung) | High thoracic | Paraplegia | Amph. B 5-fluoro Miconazole | — | Healed, except bilateral Babinski |
| 24 (11) M 6 y | + | Fumig. | Contig. (lung) | Upper thoracic | Paraplegia | Bone marrow transplant Amph. B | — | Healed with a drop foot |

| Case n° Reference Sex Age | Diminished immunity | Strain | Spread | Level | Clinical picture | Antibiotics | Spinal surgery | Outcome |
|---|---|---|---|---|---|---|---|---|
| 25 (14) M 71 y | — | Terreus | Contig. (vascular graft) | L2L3 | Back pain | Amph. B | — | Died |
| 26 (15) M 44 y | + | Fumig. | Hematog. (lung) | L2L3 | Back pain | Amph. B | — | Died |
| 27 (20) M 9 y | + | Fumig. | Contig. (lung and rib) | T1T2 T5T7 | Back pain | Bone marrow transplant | — | Partial cure |
| 28 (21) M 6 y | — | Nidul. | Contig. (lung and rib) | T1 to T8 | Back and girdle pain Pyramidal | Amph. B | — | Died |
| 29 (22) M 54 y | ± | Flavip. | Hematog. (pulm. artery catheter) | L3L4 | Back pain + bilateral sciatica | Amph. B | — | Healed |
| 30 (25) M 13 y | — | Fumig. | Hematog. (finger wound) | T4T5 T10T11 L3L4 | Back pain | KI Cod-liver oil Radiation | — | ? |
| 31 (26) M 0,5 y | — | ? | Contig. (lung) | T3T4 | Paraplegia | ? | — | Died |
| 32 (31) ? 4 y | + | Fumig. | Contig. (lung and rib cage) | T3T4 | Paraparesis | Amph. B Mycostatin and classical antibiotics | — | Died of bilateral necrotizing pneumonia |

3% ; species not reported in 3 cases. Spread to the vertebrae occurred via direct inoculation in 6 cases or 19%, via contiguity in 15 cases or 47%, via the bloodstream in 10 cases or 31% ; unknown in one case. The most frequently involved levels were the upper thoracic and the middle lumbar vertebrae. The cervical spine was never affected.

The clinical picture consisted of back pain or sciatica in 18 cases or 56%, and unilateral or bilateral paresis or paralysis of the lower limbs in 14 cases or 44%. The sedimentation rate rose to an average of 92 mm, range "normal" to 135 mm, at least in the 16 cases where it was mentioned. The white blood cell count was 10,215 per $mm^3$ on an average, range "normal" to 20,000 ; it was mentioned in 18 cases. The temperature was 38.3° Celsius on an average, range "normal" to 40° ; it was reported in 17 cases.

Radiographic examination showed vertebral osteolysis in all cases, a paravertebral abscess in 3, a partial myelographic block in 7 cases, and a complete block in 4 cases.

Serology was performed in 11 cases. Either antibodies or antigens were determined, each in about

50% of the cases. Two tests were false negative ; one of these was probably due to lowered immunity.

A needle biopsy was performed in 11 cases or 34% ; an open biopsy (vertebrae, rib or lung) in 14 cases or 44% ; both techniques were used in 4 cases or 13% ; a lung aspirate led to the diagnosis in 2 (6%) ; in one case (3%) a biopsy was not mentioned. Positive cultures were specifically reported in all cases but one. The presence of the typical hyphae was histologically confirmed in 19 cases or 59%.

Combined operative-medical treatment was used in 20 patients or 63%. Of these, 14 or 70% survived. Eight or 40% of this subgroup had major neurological involvement of the lower limbs ; possibly one or 13% of this subgroup recuperated. Purely medical treatment was preferred in 12 patients or 37%. Of these, 6 or possibly 7 survived : maximally 58% of this subgroup. Five or 42% had major or neurological involvement, which is comparable with the former group ; 2 recuperated, or 40% of this subgroup.

We attempted to correlate survival with various factors. Seven out of 21 patients with diminished immunity, or 33%, died, versus 3 out of 11 with normal immunity, or 27%. The age of the surviving patients was 41 on an average, versus 38.2 for the others. Seven out of 23 men, or 30%, died ; 3 out of 8 women, or 38%, died. The various fumigatus species were not distinctly correlated with survival or death. Thoracic involvement led to death in 6 out of 17 patients, or 35% ; lumbar involvement in 5 out of 15 patients, or 33%. Severe neurological involvement was present in 13 patients, 5 of whom died (46%). Slight or no neurological involvement was noted in 19 patients, 5 of whom died (29%). All 3 patients in whom itraconazole was used, either alone or in combination with other modes of treatment, survived.

## DISCUSSION AND CONCLUSION

Survival of patients with invasive aspergillosis is quite variable : 35 to 45%, according to Fisher (12), 87% according to Burch (5). In this series on vertebral aspergillosis 21 out of 32 patients survived, or 66%. Of course it is impossible to compare entirely different series.

More interesting is the question of how the results can be improved. Tack (27) feels that analogy with bacterial osteomyelitis should suggest that combined medical-surgical therapy is superior to purely medical treatment. At first sight this seems to be confirmed by the present study, where the survival was respectively 70% and 58%. However, neurological recovery was much more frequent in the "medical" group : 40% versus 13% in the "combined treatment" group. In fact it was impossible to state which of both treatment groups was most severely affected. Indeed, the combined approach might have been chosen because of the local severity of the disease. But on the other hand medical treatment might have been preferred in some cases because of the poor general condition. It seems thus inappropriate to state that either of the treatments is superior. Diminished immunity, age, sex, fumigatus species, and level of involvement were not distinctly correlated with survival or death. Severe neurological involvement was definitely unfavorable, but this is a well-known fact. Itraconazole seems promising, but 3 cases are not enough to warrant exaggerated optimism.

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## SAMENVATTING

*K. D'HOORE, M. HOOGMARTENS. Vertebrale aspergillosis. Een gevalstudie en literatuuroverzicht.*

Een geval van Aspergillus osteomyelitis van de wervelkolom wordt besproken. Een literatuurstudie leverde 31 bijkomende gevallen op, wat het totaal op 32 brengt. Aspergillus osteomyelitis is zeldzaam, maar de wervelkolom wordt het meest frequent aangetast. Ze kan ontstaan langs hematogene weg, per contiguitatem, of door rechtstreekse inoculatie. Tot op heden steunde de medicamenteuze behandeling op amphotericine B, maar de toxiciteit hiervan is problematisch. Itraconazole en fluconazole hebben dit nadeel niet. Een aanvullende heelkundige behandeling werd vroeger reeds aangeraden door sommige auteurs. In de voorliggende serie leidde een medicamenteus-heelkundige behandeling (20 gevallen) inderdaad tot een hoger overlevingspercentage (70%) dan de zuiver medicamenteuze behandeling (12 gevallen : 58%). Deze laatste stond echter in voor een beter neurologisch herstel (40% tegen 13%).

## RÉSUMÉ

*K. D'HOORE, M. HOOGMARTENS. Aspergillose vertébrale. Cas clinique et revue de la littérature.*

Un cas d'Aspergillose vertébrale est présenté. Trente-et-un cas supplémentaires ont été décrits dans la lit-

térature, soit un total de 32 cas. L'ostéomyélite à Aspergillus est rare, mais la localisation rachidienne est la plus fréquente. Elle peut relever de 3 mécanismes : par voie hématogène, par contiguité, ou par inoculation directe. Jusqu'à présent le traitement a reposé sur l'administration d'amphotéricine B, mais la toxicité pose des problèmes. L'itraconazole et la fluconazole n'ont pas ce désavantage. Certains auteurs ont conseillé un traitement médico-chirurgical. Celui-ci (20 cas) a assuré une survie de 70% dans la série présente, contre 58% pour le traitement médical (12 cas). Ce dernier a cependant donné de meilleurs résultats du point de vue neurologique (40% contre 13%).