Haematologica 1998; 83:1116-1119 case of the month

Ocular presentation and successful outcome of invasive sphenoid sinus aspergillosis in acute myelogenous leukemia

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ABSTRACT

We report the case of a 73-year-old male with acute myelogenous leukemia, who progressively developed a cavernous sinus syndrome during the aplastic phase after induction chemotherapy. Although the clinical, serological and radiological findings suggested an invasive sphenoid sinus aspergillosis, endoscopic ethmoido-sphenoidectomy allowed definitive diagnosis of the infection. After surgery, fungal eradication and reversal of the neurophtalmological damage paralleled complete hematologic remission. The differential diagnoses of the patient ocular symptoms are discussed. Early recognition, prompt intervention and immunologic reconstitution are essential for successful outcome of paranasal mycoses in immunosuppressed patients.

Key words: acute myelogenous leukemia, fungal infection, invasive sphenoid sinus Aspergillosis, ophthalmoplegia

A 73-year-old white male was referred to the neuro-ophthalmology service of our hospital in late November 1997 for unexplained painless visual loss in the left eye first noticed on wakening in the morning. The patient had a long history of hypertensive heart disease which was managed with captopril and hydrochlorothiazide. There was no history of malignancy, diabetes or coagulopathy. Visual acuity in the left eye was 20/100. Cranial nerve testing was normal except for a 2+ afferent pupillary defect on the left side. Slit lamp examination revealed a mild nuclear cataract. Funduscopic exam evidenced a central retinal vein occlusion (CRVO) in the left eye with diffuse hemorrages at the posterior pole. Routine screening exams showed a pancytopenia with the following values: white blood cell (WBC) count 0.9×10^9/L (neutrophils 20%, lymphocytes 76%, monocytes 4%), red blood cell count 2.48×10^{12}/L, hemoglobin 7.6 g/dL, platelet count 99×10^9/L. Blood chemistry values were within normal range. Coagulation tests were normal.

The patient was admitted to the Hematology Department. On admission his temperature was 36.6°C, blood pressure 140/80 mmHg and heart rate 84 bpm. Physical examination was normal except for pallor and liver enlargement. Bone marrow (BM) aspirate showed trilineage dysplasia with 40% myeloblasts immunophenotypically $CD43^+$, $CD33^+$, $CD11c^+$, and $HLA\text{-}DR^+$. Cytogenetic studies on BM blood showed a 45,XY,del(6)(q16),–7 karyotype in 19/21 Q-banded metaphases analyzed. Chest X-ray was negative. Abdominal ultrasound confirmed a mild hepatomegaly. The patient was diagnosed as having acute myelogenous leukemia, type M2 according to FAB criteria.

Induction chemotherapy with cytosine arabinoside (200 mg/m^2 i.v. for 5 days) and mitoxantrone (12 mg/m^2 i.v. for 1 day) was started. Antibacterial and antifungal oral prophylaxis with ciprofloxacin 500 mg twice a day and fluconazole 100 mg daily was associated with inhaled amphotericin B 15 mg twice a day. Clinical presentation, laboratory findings and treatment are reported in Figure 1. Two weeks after admission, fever appeared. Ceftazidime and amikacin instead of ciprofloxacin were started for presumed bacterial infection.

During the third week, the patient complained of left frontal and periocular pain with occipital irradiation. A neurological consultation confirmed trigeminal neuralgia in V_1 and V_2. Ophthalmologic slit-lamp examination was unremarkable. Intra-ocular pressure was within normal limits. Erythrocyte sedimentation rate (ESR) was 28 mm/h. The most common ocular causes (acute glaucoma, uveitis) potentially responsible for the referred symptomatology were therefore excluded. A negative clinical history and the normal ESR made temporal arteritis unlikely. The absence of previous similar symptoms and old age excluded a cluster headache.

Since the fever persisted, fluconazole was empirically replaced by oral itraconazole 600 mg daily. Seven days later the patient developed left ptosis due to partial III nerve ophthalmoplegia which became complete during the following 24 hours, with involvement of the ipsilateral IV and VI cranial nerves.

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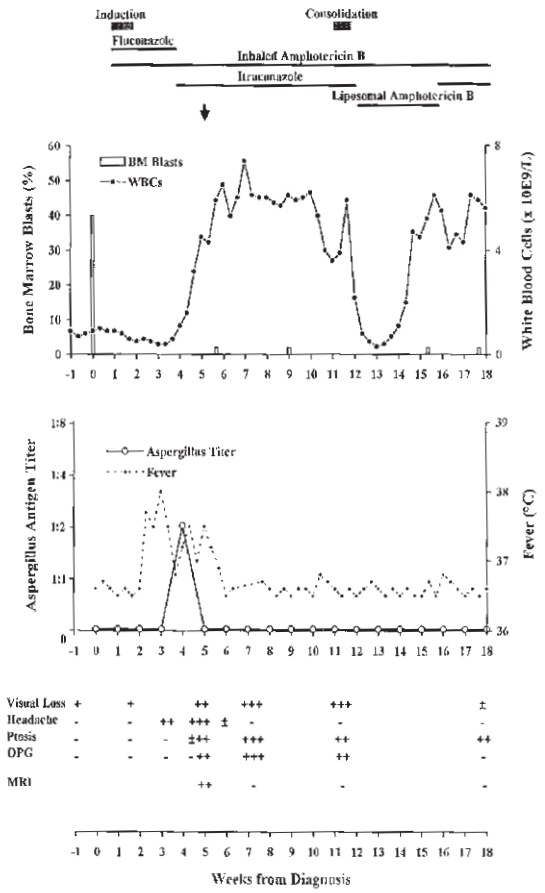

Figure 1. Clinical findings, laboratory parameters and treatment of the patient. The arrow indicates the ethmoido-sphenoidectomy. BM, bone marrow; WBCs, white blood cells; OPG, ophthalmoplegia; MRI, magnetic resonance imaging.

Visual acuity further deteriorated to 20/200. A typical cavernous sinus (CS) syndrome was evident. The presence of a tumor was excluded by the rapidity of the neuro-ophthalmological changes. Computed tomographic (CT) scanning and magnetic resonance imaging (MRI) were needed to identify the cause of the acute onset of CS syndrome (differential diagnoses were carotid artery aneurysm, carotid-CS fistula or inflammatory processes).[1]

The CT scan showed that the left sphenoid sinus was entirely filled by chronic inflammatory tissue with calcifications resulting in focal areas of increased intensity (Figure 2). On spin-echo T_1 MRI the sinus appeared hypointense (Figure 3), while on T_2-weighted images the sinus contents returned a bright signal. Gadolinium injection showed a peripheral rim enhancement of the sinus and compression of the left optic nerve at the optic canal. MR angiogram excluded vascular abnormalities. By that time, results from serologic studies performed 1 week previously had become available; they showed positivity for Aspergillus antigen at a low titer (1:2).

The differential diagnosis of sphenoid sinus disease includes bacterial or fungal sinusitis, a mucocele, and malignant or granulomatous diseases.[2,3] Bright T_2 weighted images on MRI confirmed the presence of an inflammatory process in our patient rather than a tumor, which is characterized by a low to intermediate T_2 signal.[3,4] The patient's myelosuppression and the acute development of ocular symptoms suggested fungal sinusitis.[5] Absence of diabetic ketoacidosis

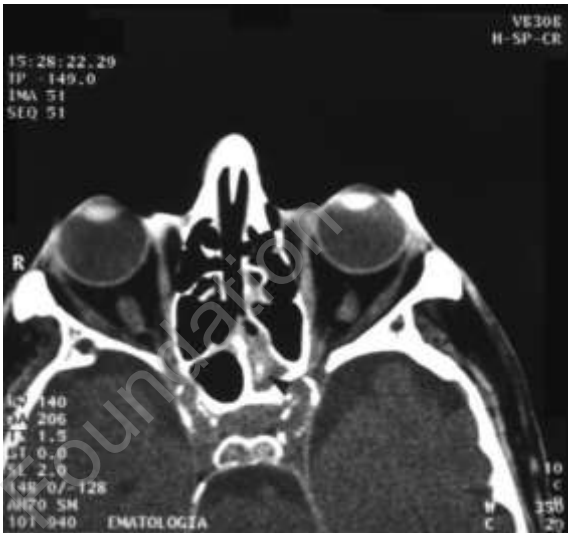

Figure 2. CT scan on an axial neuro-ocular plane showing the left sphenoid sinus entirely filled by a chronic inflammatory tissue with calcifications, resulting in focal areas of increased intensity (arrowhead).

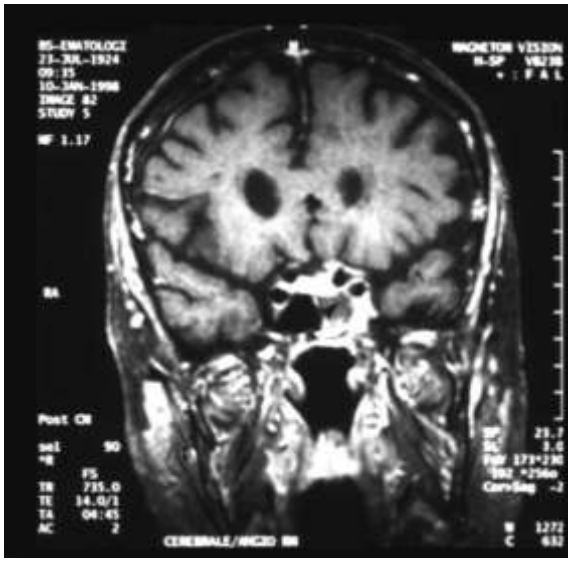

Figure 3. Spin-echo T1 MRI on a coronal plane showing an opacified, hypointense left sphenoid sinus with a small component of intensity similar to that of the muscle (arrowhead).

made the involvement of Mucor unlikely.[6] Indeed, CT detection of calcifications inside the opacified sinus and a raised Aspergillus titer strongly indicated sphenoid sinus Aspergillosis.[7,8]

At that time, the values of WBCs had returned to normal and BM aspirate showed a complete hematologic remission. Functional endoscopic ethmoidosphenoidectomy was immediately performed under local anesthesia. Necrotic fluid and debris were drained and the left sphenoid sinus was aerated. Histologic examination of the removed material showed a predominantly granulomatous response with fibrosis and tissue necrosis. Cultures grew *Aspergillus fumigatus*.

The typical patterns of paranasal sinus aspergillosis in immunosuppressed patients are the invasive and fulminant forms.[6,9,10,11] Fulminant aspergillosis is consistent with a rapidly progressive gangrenous mucoperiostitis leading to destruction of sinuses within a few days and a fatal outcome; histologic examination readily shows hyphae combined with necrosis and little inflammatory response.[11] In our case, the relatively indolent clinical course and the histologic finding of a granulomatous response were suggestive of an invasive form.[10]

After surgery, the pyrexia disappeared and seroconversion of Aspergillus antigen occurred. One week later the trigeminal headache had disappeared. However, neither ocular motility nor visual acuity improved. The patient was discharged on oral itraconazole and inhaled amphotericin B. During follow-up, serum antigenemia tests remained negative; ophthalmological evaluation revealed a counting-fingers visual acuity and a total left external ophthalmoplegia; MRI showed no sign of recurrent sinus infection.

Eleven weeks after diagnosis the patient started consolidation chemotherapy (cytosine arabinoside 200 mg/m^2 i.v. for 5 days and daunoxome 80 mg/m^2 i.v. for 1 day). Due to the gastrointestinal toxicity of the therapeutic regimen, itraconazole was temporarily replaced by i.v. liposomal amphotericin B 2 mg/kg daily. During hospitalization, neither clinical nor serological evidence of fungal infection recurrence was recorded. Four weeks after the start of consolidation treatment, WBCs recovered and complete remission of the acute leukemia was documented.

On April 1998, 18 weeks after diagnosis, the patient was doing well in a continuous hematologic remission; III nerve paralysis persisted, but visual acuity had improved to 20/50 with complete recovery of the IV and VI left cranial nerves; funduscopic exam was unremarkable; MRI showed an empty, air-filled left sphenoid sinus.

Discussion

Invasive mycoses are common life-threatening complications in patients with hematologic malignances.[12-16] Paranasal sinus involvement is reported in the most severe form.[15,16] Myelosuppression may predispose to the *ex novo* development of an invasive fungal sinusitis, trigger the progression of a silent to an invasive form or reactivate the fungus after an apparently curative antimycotic treatment.[14,15]

Aspergillosis is the most commonly reported mycosis and usually affects the maxillary and ethmoidal sinuses, whereas involvement of the sphenoid sinus is rare.[6] Detection of the fungus is problematic; isolation of Aspergillus from respiratory secretions is difficult and often not specific.[17] Biopsy of the affected tissue may yield the fungus but is frequently difficult to perform in pancytopenic patients. Aspergillus antigenemia might identify infected patients,[8] but its significance in paranasal sinus aspergillosis has not yet been established.

Patients with sphenoid sinus disease have non-specific complaints, headache being the most common. Rhinorrhea, ptosis, proptosis, diplopia and decreased visual acuity are also frequently reported.[18-20]

Although in our case a clear CS syndrome paralleled serological and clinical suspicion of fungal infection, an earlier left CRVO was responsible for the initial visual loss. The patient had no risk factor for thrombosis such as blood hyperviscosity, and hypertensive retinopathy was not present despite the systemic hypertension. The left CRVO might have been the first sign of an initially expanding Aspergillus mass at the superior orbital fissure level, exerting pressure effect on the superior orbital vein without ocular congestion. Trilineage dysplasia and the complex karyotype of leukemic blasts were suggestive of a pre-existent myelodysplastic syndrome; long-standing neutropenia prior to referral might have facilitated fungal growth.[5] However, in the absence of early radiological examinations, the correlation between the initial ocular presentation and the subsequent Aspergillus sinusitis remains uncertain.

Sphenoid sinus aspergillosis is more aggressive than other sinus infections because of the close relationship with the skull base.[11] Vessels may act as direct channels for the seeding of Aspergilli and erosion of bone is not always necessary for the development of intracranial extension. Thus, early recognition is important to prevent a fatal outcome. Wide debridement and systemic antimycotic treatment are recommended.[6,18,21] Itraconazole has been successfully used to treat invasive Aspergillosis due to its specific activity against Aspergillus species.[21,22] However, this drug seems to be less effective in sinus infections than in infections of other sites.[22] In accordance with previous reports,[21,22] we used itraconazole as systemic antimicrobial support for the surgery. However, since this antifungal therapy was started around the time of neutrophil reconstitution and surgical treatment, it is hard to evaluate the contribution it made to our patient's improvement.

Visual function outcome is mainly related to the precocity of both diagnosis and treatment, the earli-

er the latter, the better the prognosis. Indeed, tissue infarction resulting from fungal blood vessel invasion might be responsible for early irreversible damage. Moreover, when visual impairment is caused by orbital diffusion of the mycosis, the ocular prognosis is awful.[23] Although in our case visual function was not restored immediately after surgery, a progressive recovery of both visual acuity and ocular motility was observed over three months. Liposomal amphotericin B administered during consolidation might have aided the post-surgical improvement. However, the premature establishment of persistent third nerve damage suggests that the intervention should not have been delayed more than 48-72 hours after the patient's first complaint.

In conclusion, neutropenic patients with fungal sinusitis may present with aspecific ocular signs or symptoms that need careful evaluation. Appropriate diagnostic and therapeutic tools must be used promptly in order to avoid long-term neuro-ophthalmological injury and a fatal outcome.

Contributions and Acknowledgments

Both AC and CC followed the patient clinically, were primarily responsible for the conception of this paper, and equally contributed to the manuscript writing. Authors are mentioned in alphabetical order.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received May 7, 1998; accepted September 8, 1998.

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