Bipolaris spicifera Causes Fungus Balls of the Sinuses and Triggers Polypoid Chronic Rhinosinusitis in an Immunocompetent Patient

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We report the rare case of a 19-year-old immunocompetent male suffering both from fungus balls of the sinuses and from chronic rhinosinusitis with massive polyposis. Endoscopic sinus surgery revealed grayish brown necrotic masses embedded in viscous eosinophilic mucus. Inoculated onto petri dishes, these masses as well as the mucus grew a dark pigmented fungus, which was identified as Bipolaris spicifera.

CASE REPORT

A 19-year-old immunocompetent (human immunodeficiency virus negative, no evidence for malignancy) man was referred to our clinic because of restricted nasal breathing for 1 year and total nasal obstruction for more than 4 months. Computed tomography scan revealed massive sinusitis, with significant decalcification and destruction of the bone at skull base. Polyps and fungal masses had elevated the dura and extended far intracranially, especially in the frontal recess region and the roof of the anterior ethmoid. The dura appeared to be pushed against the brain for more than 1 cm on both sides (Fig. 1). On magnetic resonance imaging, however, there appeared to be no infiltration or penetration of the dura. Endoscopic examination showed a total obstruction of both nostrils with glasy polyps. Immunological examination of the patient’s blood showed a highly elevated level of total immunoglobulin E (IgE) (4,446 kU per liter (kUL⁻¹); normal value, <100 kUL⁻¹). Specific IgE tests (UniCAP; Pharmacia, Uppsala, Sweden) yielded classes 3 and 4 for all fungal allergens tested (Table 1) (13). The highest responses were provoked by Penicillium notatum (30.3 kUL⁻¹), Helminthosporium halodes (Escherichium rostratum; 20.3 kUL⁻¹), Mucor racemosus (19.4 kUL⁻¹), and Alternaria alternata (14.2 kUL⁻¹). Clinical chemistry showed no abnormalities in electrolytes, substrates, enzymes, and proteins, blood coagulation parameters were also in the normal range. The differential white blood cell count indicated significant eosinophilia (20% of leukocytes, 1 billion per liter); the basophil levels were also elevated slightly (1.6%).

Endoscopic sinus surgery of both sides was performed by using VTI-Navigation (Visualization Technology, Inc./GE Medical Systems, Lawrence, Mass.). On the left side, the patient presented with a massive polyposis, with polyps protruding as far as the nasal vestibulum. Mucus masses were aspirated first and preserved for mycological examination. Then, in a stepwise fashion, the anteriormost polyps were removed until a huge mucocele of the concha bullosa of the middle turbinate was identified. This mucocele reached almost to the nasal vestibulum and filled most of the nasal lumen. When opened there were massive polyps with glue-like mucus and fungal masses inside the concha. Then, in a stepwise fashion, preparation was taken further posteriorly and up, until in the posterior ethmoid skull base could be identified. Laterally, the polyps and fungal masses had protruded significantly (8 to 10 mm) toward the orbit; the bony border was missing partially. Only with navigational support was it possible to avoid all of the areas of hazard in this distorted anatomy. Removal of the glue-like inspissated material was extremely difficult and time-consuming. The sphenoid sinus was then identified and opened; it, too, was filled with polyps and fungal masses (Fig. 2), which were peeled off the carotid artery, the optic nerve, the floor of the sella, and the clivus. Preparation was taken anteriorly following the skull base; these regions were tightly packed with polyps and glue-like fungal material. There was dura exposed; upon palpation, thin bony layers could still be identified. From there, the surgery was moved toward the frontal sinus, where the same situation was encountered: the sinus was expanded from polyps and fungal masses like a balloon. Altogether, it took 3 h to remove, aspirate, and irrigate all this material out of the frontal and adjacent recesses. Then, the maxillary sinus ostium was identified and here, too, the same viscous material was removed. The remaining portion of the middle turbinate was trimmed, and hemostasis was carefully achieved. The right side of the nose presented almost the same situation. Finally, large Rapid-Rhino nasal sinus dressings (Applied Therapeutics, Tampa, Fla.) were inserted bilaterally. Postoperative medication consisted of systemic antifungal agent (itraconazole, two 100-mg doses per day for 6 weeks, followed by one 100-mg dose per day for 8 weeks) and both systemic (betamethasone) and topical (budesonide) steroid therapy. Furthermore, nasal douches with saline were recommended to eliminate excess mucus.

Histology. Histological examinations of formalin-fixed and paraffin-embedded tissue and mucus samples were performed. Hematoxylin and eosin (H&E) staining revealed inflammatory sinonasal polyps and clusters of eosinophilic granulocytes within the mucus. Gomorri methenamine silver (GMS) staining showed septate fungal hyphae not only in the fungal masses (fungus balls) but also within the mucus, where the hyphae seemed to be impacted or embedded within the clusters of
eosinophils (Fig. 3). A fungal invasion of the tissue was not observed.

Mycology. Mucus and fungus balls were cultured after mucolytic treatment as described recently (3). The colonies on Sabouraud dextrose agar at 25°C were fast growing, reaching a diameter of 4 cm in 7 days, and presented as velvety, brownish, and flat. Microscopy revealed septate pigmented hyphae and unbranched zigzagged conidiophores with thick-walled, darkly pigmented cylindrical conidia, which were predominantly three septate. Due to these characteristics, the fungus was identified as Bipolaris spicifera (Bain.) Subram. To confirm the identity, nuclear DNA both from cultures and from native concrement was extracted, PCR of the internal transcribed spacer region of the ribosomal gene cluster was carried out with fungus-specific primers, and the resulting amplicons (575 bp) were sequenced as described previously (2, 3). The sequence data were compared to entries in GenBank, and there was 100% identity with Cochliobolus spiciferus Nelson, which is the teleomorph of Bipolaris spicifera. Sequence data were submitted to the National Center for Biotechnology Information, where it was assigned accession number AY253918.

The fungal strain itself was deposited at the Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands (strain number CBS 113180).

**Discussion.** The dematiaceous fungus Bipolaris spicifera is often named in the literature as one of its synonyms, which can lead to confusion. The names Curvularia spicifera, Brachycladium spiciferum, Drechslera spicifera, and Helminthosporium spiciferum are obsolete synonyms, whereas Cochliobolus spicif-
erus is the teleomorph of this species (16). Bipolaris spicifera appears frequently in medical literature as a cause of diseases in humans and animals. Besides cutaneous and subcutaneous phaeohyphomycoses (15, 31), a meningitis (12), fungemia in children infected with human immunodeficiency virus (32), disseminated infection (9), a mycotic keratitis (8), a fatal fungal endarteritis (21), and disseminated infection in a neonate (17), most of the cases where Bipolaris spicifera is involved are pertaining to the nasal sinuses (6, 14, 16, 20, 23, 25, 26, 27, 28, 29, 30). Interestingly, many of these cases were encountered in areas where a hot climate is predominant (Texas, South Carolina, Arizona, and Georgia in the United States; Brisbane, Australia; Pakistan; and India). Schubert made the same observations and actually reported Bipolaris spicifera to be the most common cause of allergic fungal sinusitis in the southwestern United States (27, 28). Our patient was a resident from Kuwait, where very hot, dry summers and mild winters characterize the climate. Investigations of the fungal flora in Kuwait showed that Bipolaris spp. are among the most frequent airspora encountered. The numbers vary between 2.8% (7), 3.4% (18), 10.6% (10), and 14% (19), depending on the location and the season. This incidence is much higher compared to results of air sampling in middle Europe, where Bipolaris spp. are found only between 0 and 0.2% of the total CFU (4, 5, 11, 24). In a recently published study of the biodiversity of fungi in the nasal mucus samples of 234 patients with chronic rhinosinusitis, Bipolaris hawaiensis was isolated in 2 patients and Bipolaris australiensis was isolated in another; these patients were from the Middle East and from India, respectively (3).

Fungi seem to play a major role in the pathogenesis of chronic rhinosinusitis, as recent studies suggest (1, 22). An overshooting response of eosinophilic granulocytes against fungi rather than allergy (IgE mediated) is the proposed mechanism of this chronic inflammation. Nevertheless, our patient presented a very high level of total IgE (4,446 kU/L). Specific IgE was elevated for all fungal allergens tested, the highest for Alternaria alternata (14.2 kU/L). There was no allergen test available for Bipolaris spicifera.

When stained with GMS, parallel sections of the paraffin-embedded mucus showed fungal hyphae and clusters of eosinophils in the corresponding H&E-stained slides, suggesting the entity of an eosinophilic fungal rhinosinusitis as described by Ponikau et al. (22), combined with mycoses of all nasal sinuses (fungus balls). This is a rarely encountered combination of two commonly different diseases found in the same location and caused by the same pathogen, Bipolaris spicifera.

REFERENCES


