Invasive aspergillosis of the nose and paranasal sinuses is one of the presentations of aspergillosis in granulocytopenic patients with neoplastic disorders. It is most prevalent among patients with leukemia and granulocytopenia and is associated with a high mortality rate. We report five cases of invasive aspergillosis of the nose and paranasal sinuses in profoundly neutropenic patients treated with broad spectrum antibiotics. Both *Aspergillus fumigatus* and *Aspergillus flavus* were cultured and identified in this entity. Awareness of this disease and early diagnosis made by culture and histologic examinations of biopsy material are essential. Treatment consisting of amphotericin B therapy and surgical debridement can be effective in eradicating this form of aspergillosis.

**ASPERGILLOSIS OF THE NOSE AND PARANASAL SINUSES IN NEUTROPENIC PATIENTS AT AN ONCOLOGY CENTER**

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Invasive aspergillosis has been reported with increasing frequency in recent years among cancer patients and other immunocompromised patients. It is the second most common fungal infection in patients with malignant disorders. *Aspergillus* is ubiquitous in the environment, and significant environmental exposure to *Aspergillus* can lead to invasive disease in patients with neoplastic disorders. Invasion of lung parenchymal tissue and blood vessels follows colonization of the tracheobronchial tree by inhaled *Aspergillus* spores in immunocompromised cancer patients. Pulmonary involvement is present in almost all cases of invasive aspergillosis seen in this patient population.

Although a variety of forms of invasive aspergillosis are commonly seen in the lower respiratory tract, *Aspergillus* rarely invades the upper respiratory tract in immunocompetent individuals. Invasive aspergillosis of the nose and paranasal sinuses (IANPS) has been described in about 170 people (exclusive of the Sudan, where it is endemic), including 28 patients with malignancy. Although it is not commonly seen in individuals with neoplastic diseases and neutropenia due to cytotoxic therapy, this form of aspergillosis is particularly serious, resulting in high mortality. We report five patients with IANPS who were clustered in a 1-year period, describe their diagnosis and treatment, and make some recommendations for the diagnosis, treatment, and possible prevention of this entity.

**PATIENTS AND METHODS**

Over a 1-year period, four patients with leukemia and one with aplastic anemia were hospitalized at Roswell Park Memorial Institute (RPMI). All patients were profoundly neutropenic (<100 neutrophils/mm³). The patients with leukemia were rendered neutropenic by the administration of cytosine arabinoside (ara-C) with or without meta-“n4”-acridinyl amino-3-“methoxphenyl” methansulfuramide (m-AMSA) (three patients) or a bone marrow transplant conditioning regimen of cyclophosphamide, ara-C, and total body irradiation (one patient). The patient with aplastic anemia received anti-thymocyte globulin (ATG) and large doses of prednisone (60 mg/day) as treatment for his disease.
Each patient was followed by the Infectious Diseases and Head and Neck services of RPMI. Biopsies of nasal tissues were performed by the Head and Neck service on four of the five patients. In these four cases, IANPS was defined as the presence of characteristic, acutely branching, septate hyphae invading mucosal tissue on pathologic examination of hematoxylin and eosin, periodic acid-Schiff, or methenamine silver stained mucosal biopsy material with or without the growth of *Aspergillus* sp. on Sabouraud dextrose agar or mycosel agar from the tissue biopsy material. The fifth case was defined as the presence of the typical clinical presentation of IANPS (erythema and swelling of the nasolabial fold, with facial and periorbital cellulitis, nasal drainage, and involvement of the maxillary sinus) and the growth of *Aspergillus* from the nares and nasal discharge.

Morphologic identification of *Aspergillus* was accomplished with lactophenol cotton blue staining. Identification of the isolated *Aspergillus* organisms was performed by the Division of Laboratories and Research of the New York State Department of Health, Albany, New York.

Autopsy findings were reviewed and correlated with the clinical course of the disease whenever possible.

**CASE REPORTS**

**Patient 1.** A 33-year-old man with recently diagnosed aplastic anemia was transferred to RPMI for further therapy and consideration for bone marrow transplantation. The patient was treated with ATG 2 mg/kg/day for 7 days. Two weeks after ATG therapy, serum sickness developed and prednisone 60 mg/day was administered. One week later the patient developed *Pseudomonas aeruginosa* perineal cellulitis with bacteremia. Piperacillin and tobramycin were initiated. His neutrophil count was <100/mm³ at this time.

During the sixth week of hospitalization, while his total white blood cell (WBC) count was 700/mm³ (100% lymphocytes), a red and tender swelling of the right nasolabial fold appeared (Figure 1). Culture of a nasal mucosa biopsy specimen grew *A. flavus*. Histologic examination of the biopsy revealed invading septate hyphae consistent with *Aspergillus*. Amphotericin B (1.2 mg/kg/day) was given intravenously in combination with rifampin (600 mg/day). Subsequently, swelling of the right side of his face increased. Nasal examination revealed destruction of the anterior portion of the right inferior turbinate. A computed tomographic (CT) scan of the nose and paranasal sinuses (which had been negative on the first day of clinical signs) showed a complete opacification of the right maxillary sinus (Figure 2). It was decided that drainage of the sinus was necessary, and an antrotomy (Caldwell-Luc procedure) and an inferior turbinectomy were performed (Figure 3). The drains were left in his maxillary sinus through which irrigation of amphotericin B (amphotericin B 20 mg in 50 cc dextrose and water twice a day) was performed. Intravenous amphotericin B 1.2 mg/kg/day was continued. An attempt to increase the amphotericin B dosage to 1.5 mg/kg/day failed due to impairment of renal function. Gradual improvement in the edema and erythema of the right nasolabial fold and a marked decrease in the opacification of the right maxillary sinus ensued. The patient was discharged from the hospital 38 days after operation. The patient's WBC count began to rise 20 days postoperatively and peripheral WBC count at discharge was 1700/mm³, with 26% segmented forms, 2% monocytes, and 54% lymphocytes. Amphotericin B was continued intrave-
FIGURE 2. CT scan of patient with invasive aspergillosis of maxillary sinus demonstrating opacification of the right maxillary sinus.

FIGURE 3. Methenamine silver stain of the right inferior turbinate demonstrating tissue invasion by the branching septate hyphae of *Aspergillus*. (Magnification × 240).
nously as an outpatient to a total of 4 g. Ten months after discharge, the patient is left with a minimal oroantral fistula. There is no evidence of recurrence of IANPS.

**Patient 2.** A 36-year-old woman with a 12 year history of chronic myelogenous leukemia (CML) was found to be in blastic phase and was hospitalized for a bone marrow transplant. The patient was conditioned with cyclophosphamide, ara-C, and total body irradiation. Four days after receiving an allogeneic bone marrow transplant, the patient developed a fever of 38.5°C. Carbenicillin and tobramycin were initiated. Seven days posttransplant, mucositis of her mouth developed and acyclovir was added to her regimen because of herpetic stomatitis. One week later, with her total WBC count remaining at 100/mm³, the patient experienced a red and tender swelling of her left nasolabial fold, which progressed rapidly and spread over the left maxillary area during the following days. X-ray films of her face and paranasal sinuses revealed only soft tissue involvement without bone destruction. Biopsy of the affected nasal area showed the typical acutely branching septate hyphae of *Aspergillus* invading the mucosa. *A. fumigatus* grew from cultures of the biopsy specimen of the left nares. The patient was treated with amphotericin B (1 mg/kg/day) intravenously and rifampin (600 mg/day). Despite this treatment, a pulmonary infiltrate of the left lung appeared on chest x-ray and progressed. Thoracotomy and partial lobectomy were performed to remove the infiltrate. The lung tissue also grew *A. fumigatus*. Postoperatively, the patient remained granulocytopenic and developed bilateral pulmonary infiltrates. Granulocyte transfusions did not provide any benefit. Marked destruction of the left nasolabial fold due to *Aspergillus* also occurred. Her condition deteriorated rapidly and she died of respiratory failure. No autopsy was performed.

**Patient 3.** A 69-year-old woman with recently diagnosed acute myelomonocytic leukemia (AMML) was admitted to RPMI for chemotherapy. The patient sustained an acute myocardial infarction on admission, which necessitated a delay in the initiation of chemotherapy. Twelve days after the administration of high dose ara-C (2 g/m² q 12 hours for 6 days) followed by m-AMSA (100 mg/m² for 3 days), the patient experienced left nasolabial swelling with an erythematous and tender area in the left paranasal area. She was being treated with carbenicillin and tobramycin at the time, and her WBC was <100/mm³. Sinus x-ray films showed opacification of the left maxillary sinus without bone destruction. Biopsy of the involved necrotic nasal area was consistent with invasive aspergillosis on histologic examination (Figure 4). Fungal cultures were negative. The patient continued to be neutropenic and was treated with amphotericin B (0.8 mg/kg/day) and rifampin (600 mg/day), but developed acute renal failure. Her general condition deteriorated and she died of acute renal failure and congestive heart failure. Necropsy findings demonstrated aspergillosis of the lungs, trachea, nose, and paranasal sinuses, and *A. fumigatus* was cultured from the left nostril.

**Patient 4.** A 38-year-old woman with a diagnosis of acute myelogenous leukemia (AML) was transferred to RPMI for further chemotherapy. One week after ara-C treatment was completed, with her WBC count remaining 100/mm³, periorbital cellulitis with conjunctivitis and proptosis of the left eye, nasal discharge, and left nasolabial fold swelling developed. A CT scan of the orbit showed a left intraorbital mass extending to the nasal vault. The mucosa of the left maxillary sinus was edematous, but no bone destruction was noted. Cultures of the left nares and nasal discharge grew *A. fumigatus*. The patient was treated with amphotericin B (dosage 0.6 mg/kg/day) intravenously, but she was persistently neutropenic. Her condition declined rapidly, and she developed bilateral pneumonia. At autopsy, *Aspergillus pneumonia* and tracheitis were found. *A. fumigatus* was grown from lung tissue.

**Patient 5.** A 53-year-old man with AML was admitted to RPMI for chemotherapy. Three weeks after receiving m-AMSA 120 mg/m² for 5 days, the patient’s WBC count was 600/mm³. An episode of fever, chills, epistaxis, and swelling with tenderness and erythema of the right side of the face developed. X-ray films and CT scan of the sinuses were normal. Broad spectrum antibiotic treatment was initiated. One week later, while continuing to be neutropenic, a black plaque was noted on the right side of the nasal septum. A biopsy of the nasal septum area was consistent with aspergillosis, but the fungal culture was negative. The patient was treated with amphotericin B (dosage 0.6 mg/kg/day) intravenously and was scheduled for surgery. On the day of surgery, the patient expelled the black plaque.
with a large sneeze. He was left with a large perforation of the septum, but the margins were negative for *Aspergillus* on biopsy. He continued to receive amphotericin B to a total of 752 mg, over 2½ weeks. His WBC rose to 3000/mm³; however, he was in relapse, with bone marrow containing 50% blasts. The patient subsequently died of *Klebsiella oxytoca* bacteremia, but no evidence of IANPS was found at autopsy.

**RESULTS**

Between January 1983 and December 1983, five patients with IANPS were seen at our institution (Table 1). Four patients were located in one particular nursing unit in different hospital rooms, while the other patient (patient 2) developed her disease on another nursing unit in a different building in the institution. The female-to-male ratio was 3:2.

All patients were profoundly neutropenic (neutrophil count <100/mm³) at the time of onset of IANPS and all patients were treated with broad spectrum antibiotics for ≥3 weeks before onset of aspergillosis. In all five patients nasal or facial swelling was the first clinical sign of IANPS (Figure 1). Physical examination of the nasal mucosa revealed ulcerated lesions in four patients. Destruction of the inferior turbinate was observed in one and septal perforation in another. Biopsy of these lesions demonstrated the histologic characteristics of tissue invasion by *Aspergillus*. Culture of the biopsy specimen was positive in only two of the patients. *A. flavus* and *A. fumigatus* were isolated, respectively. In one case (patient 4), no histologic evidence of the diagnosis was sought, but the presence of *A. fumigatus* on nasal culture with the typical clinical presentation was believed to be sufficient to confirm the diagnosis. Sinus opacification was present on plain x-ray films in three cases and on CT scan of the area (Figure 2) in three instances. An interval of 3–10 days occurred from the onset of symptoms to diagnosis and therapy in all cases.

Treatment with amphotericin B at a dosage of 0.6–1.2 mg/kg/day was administered intravenously to all patients. Rifampin 600 mg/day was added in three cases (patients 1, 2, and 3) for variable periods of time (3–10 days) with no demonstrable benefit. Surgery (Caldwell-Luc procedure) was performed in only one patient for nasal and maxillary sinus aspergillosis. Postoperatively, this patient received amphotericin B irrigations of the nose and maxillary sinus (amphotericin B 20 mg in 50 cc dextrose and water twice a day) in addition to amphotericin B intravenously. This patient was the only survivor. It is of note that his absolute neutrophil count rose to >200/mm³ after 3 weeks of treatment and was 442/mm³ at the
Table 1. Cases of invasive aspergillosis of the nose and paranasal sinuses.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patient number</th>
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<tr>
<td>Diagnosis</td>
<td>Aplastic anemia</td>
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<td></td>
<td>Acute Myelomonocytic Leukemia</td>
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<td>33</td>
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<td>Sex</td>
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<tr>
<td>Neutropenia while infected</td>
<td>+</td>
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<td>Cytotoxic drugs</td>
<td>+</td>
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<tr>
<td>Steroids</td>
<td>+</td>
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<tr>
<td>Soft tissue involvement</td>
<td>Right side of face; destruction of turbinar bone</td>
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<tr>
<td>X-ray findings</td>
<td>Maxillary sinus opacification</td>
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<tr>
<td>Cultures</td>
<td>Nose A. flavus</td>
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<td>Histologic diagnosis</td>
<td>+</td>
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<td>Broad spectrum antibiotics</td>
<td>+</td>
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<td>Antifungal treatment</td>
<td>Amphotericin B and rifampin</td>
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<tr>
<td>Outcome</td>
<td>Alive</td>
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<td>Autopsy findings</td>
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+ = Present.  
- = Not used.

time of discharge. The other patients were judged to be poor surgical candidates because of concurrent pulmonary problems. Three patients died of pulmonary involvement with aspergillosis, which appeared to develop after the onset of IANPS, and one patient with IANPS succumbed to gram-negative sepsis. In none of the latter four cases did neutrophil counts rise above 200/mm³.

**DISCUSSION**

Aspergillosis of the nose and paranasal sinuses is a relatively uncommon disease in healthy individuals exclusive of the Sudan. It may present in two distinct forms. The first is a benign or indolent form. Patients complain of stuffiness, nasal congestion, and discharge, symptoms that mimic sinusitis but do not improve with antibiotic therapy. The diagnosis is made by biopsy, and complete surgical removal of the offending organism from the paranasal sinuses is the treatment of choice.12–17

The second presentation is invasive aspergillosis of the nose and paranasal sinuses. It is characterized by invasion and destruction of the bony sinus walls, the orbit, and other soft tissues of the face,18,19 although the clinical presentation may be subtle. This form is seen in immunocompetent and immunocompromised individuals.12–21 In particular, it has been described in patients with leukemic malignancies.18–21,23 Although the mor-
mortality rate in normal individuals is \( \approx 16\% \), it approaches 80\% in immunocompromised cancer patients\(^{20}\) (present series). It is clear that IANPS can be a devastating disease in this population and may be the initial site of aspergillosis, leading to the development of pulmonary or disseminated aspergillosis.\(^{2,19,25,26}\)

Some authors have emphasized that host risk factors such as granulocytopenia,\(^{3,4}\) corticosteroids,\(^{1,5}\) and antibiotic therapy\(^{25}\) act as predisposing factors to aspergillosis. It is believed that the major host defense against Aspergillus infection is the neutrophil.\(^{27,28}\) Prolonged granulocytopenia has been identified as the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia in a controlled trial.\(^{3}\) In our series of patients with IANPS, all patients had profound neutropenia and received broad spectrum antibiotics, and two patients were treated with corticosteroids, but no controlled analysis of these factors was performed.

The spores of the ubiquitous Aspergillus, when inhaled, reach the mucous membranes of the nose and paranasal sinuses. The organism merely colonizes the upper respiratory tract in immunocompetent hosts; however, it can, under certain conditions, produce benign or invasive aspergillosis of the nose and paranasal sinuses, as mentioned above. Yet, in the granulocytopenic immunocompromised host, Aspergillus behaves quite differently. In these circumstances, it is highly pathogenic and readily invades due to the lack of neutrophil host defenses (a characteristic common to other nonpathogenic organisms that colonize neutropenic hosts). Aisner et al.\(^{25}\) have suggested that the presence of A. flavus or A. fumigatus on nose culture is predictive for subsequent or concurrent invasive aspergillosis of the lung or maxillary sinuses as acute leukemia patients. They also demonstrated that leukemic patients with A. flavus on nose culture had small ulcerating lesions high on the nasal septum which, when scraped, showed the typical branching septated hyphae of Aspergillus found on smears.\(^{25}\) We also believe that the presence of Aspergillus sp. on culture or nasal scrapings in profoundly granulocytopenic patients represents the nasal invasion of IANPS, not only a good predictor of subsequent or concurrent disease. Perhaps nasal invasion in granulocytopenic hosts is the initial portal of entry for some cases of aspergillosis,\(^{19,25}\) preceding pulmonary and/or disseminated aspergillosis, which cause high mortality in these hosts. It is of interest that we found that A. fumigatus had as much of a predilection for the upper airways as A. flavus, although Aisner and co-workers\(^{25}\) found A. flavus predominating in nasal cultures.

Early diagnosis and treatment are imperative in granulocytopenic patients with malignancy. Positive surveillance cultures of the nose for Aspergillus in profoundly granulocytopenic patients can alert the physician to the presence of IANPS. Regular examinations of the nasal cavity with scrapings of suspicious lesions for culture and histology can detect the ulcerating lesions of invasive aspergillosis of the nose. Also, early recognition of the subtle signs and symptoms of IANPS, which may be limited due to the paucity of white cell inflammatory response, will prompt the physician to obtain biopsies and culture suspicious lesions. Once the diagnosis of IANPS is proven, both surgical intervention and intravenous antifungal therapy with amphotericin B should be employed. Surgical debridement (a Caldwell-Luc for maxillary sinus involvement, an external ethmoidectomy and sphenoidotomy for ethmoid sinus involvement, a frontoethmoidectomy for frontal sinus involvement, a resection of quadrangular cartilage and vomer for nasal septum involvement, the removal of necrotic turbinates for turbinate involvement, and a debridement of the soft tissue of the nose when it is involved\(^{24}\)), with adjunctive platelet transfusions to ensure adequate hemostasis, can remove necrotic infected tissue from the nose or sinuses, allowing better penetration of antifungal therapy into the infected area.\(^{20}\) Yet, such surgery may be inapplicable due to other serious underlying medical problems of these patients. Amphotericin B irrigations of the nose and paranasal sinuses as an adjunct to systemic amphotericin B therapy may aid in eradicating the fungus and assist in the evacuation of oozing blood to prevent clot formation. The addition of rifampin to amphotericin B may prove to be beneficial,\(^{29}\) but requires further study in profoundly granulocytopenic patients with malignancy.

At present, the detection of Aspergillus antibody is not very helpful in immunocompromised hosts for the diagnosis of invasive aspergillosis but radioimmunoassay of Aspergillus antigen looks promising.\(^{30}\)

Very little clinical investigation has been performed in an effort to prevent aspergillosis in granulocytopenic patients with malignant disorders. Recently, the prophylactic use of a prepared amphotericin B nasal spray delivered by an atomizer in granulocytopenic patients with cancer has been shown to be somewhat effective in
reducing colonization (invasion) of the nose and the incidence of invasive pulmonary aspergilosis.\textsuperscript{31} The use of HEPA filtered rooms, i.e., a protected environment, has been noted to decrease the incidence of invasive aspergillosis among bone marrow transplant recipients.\textsuperscript{32} It would seem that a combination of fungal chemoprophylaxis and protected environments may be the most effective means of preventing IANPS in granulocytopenic hosts.

IANPS is a devastating disease in granulocytopenic patients with malignancy. A high index of suspicion is necessary for diagnosis. The diagnosis is made by the histologic presence of characteristic branching septate fungi with or without positive cultures, or the presence of the characteristic clinical signs. Early diagnosis and treatment with surgery and antifungal agents may diminish the mortality associated with this disease. Prophylactic intranasal amphotericin B and/or protected environments may also prove to be of benefit in these hosts.

REFERENCES