Causes of death in hyper-IgE syndrome

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Background: Hyper-IgE syndrome (HIES) is characterized by recurrent pyogenic infections, eczema, increased serum IgE levels, and a variety of connective tissue and skeletal system abnormalities. Little has been published regarding the causes of death in these patients or pathologic findings.

Objective: To identify the cause of death in patients with HIES and to describe pathologic findings in fatal HIES.

Methods: We reviewed the medical records and autopsy slides of 6 patients with HIES with autopsies performed at our institution.

Results: All 6 patients with HIES were women and ranged in age from 24 to 40 years. All patients had a history of cystic lung disease and had pneumonia at the time of death, with *Pseudomonas aeruginosa* and fungal organisms predominating. Pulmonary fungal vascular invasion with fatal hemorrhage was observed in 3 patients, and metastatic fungal disease to the brain was observed in 2 patients caused by *Aspergillus fumigatus* and *Scedosporium prolificans*. Four patients had evidence of renal tubular injury, which was likely from amphotericin B toxicity; 3 patients had glomerulosclerosis; and 1 patient had 2 kidney angiomyolipomas.

Conclusions: Our series highlights the important role *Pseudomonas* and *Aspergillus* species play in patients with HIES with cystic lung disease. Intensified antifungal and gram-negative bacterial prophylaxis need evaluation as possible strategies to prevent these infectious complications in patients with cystic lung disease.

Clinical implications: Fungal and *Pseudomonas* infection of cystic lung disease in HIES may be life threatening, and the proper management and prevention of these infections need continued investigation. (J Allergy Clin Immunol 2007;119:1234-40.)

Key words: Aspergillus, *hyper-IgE syndrome, immunodeficiency, pneumonia,* Pseudomonas

Abbreviations used
CT: Computed tomography
GMS: Gomori methenamine silver
HIES: Hyper-IgE syndrome
LAM: Lymphangioleiomyomatosis
MRI: Magnetic resonance imaging
NIH: National Institutes of Health

The hyper-IgE recurrent infection syndrome (HIES), or Job's syndrome, is a rare primary immunodeficiency characterized by extremely increased serum IgE levels, eczema, recurrent infections, and a variety of connective tissue and skeletal abnormalities, including a typical facial appearance, failure to shed primary teeth, scoliosis, eczema, joint hyperextensibility, osteopenia with pathologic fractures, and craniosynostosis.[1,2] Abnormalities of the humoral, cellular, and phagocytic compartments of the immune system are all observed, but they are variable between patients and have not been fully characterized.[1,3] Recurrent skin abscesses and pneumonias result most commonly from *Staphylococcus aureus* as well as other pyogenic bacteria. After acute pneumonias, characteristic pneumatocoeles form that may become superinfected with gram-negative bacteria and fungal opportunists.[2]

No autopsy series of individuals with HIES and only limited review of pathologic specimens have been published. Therefore, we reviewed the available autopsies of patients with HIES followed at the National Institutes of Health (NIH), which is a referral center for HIES, to identify the causes of death and anatomic or pathologic correlates.

METHODS

We performed a retrospective review of the medical records, microbiology data, and autopsy slides of all patients with HIES with autopsies performed at NIH. All patients had enrolled with informed consent in approved protocols of the National Institute for Allergy and Infectious Diseases (NIAID). Under these protocols, patients were observed at least yearly at NIH, with interim visits if medically necessary. Besides a routine history and physical examination, patients were examined annually by dentistry, dermatology, and genetics. Yearly imaging included chest computed tomography (CT), brain magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DEXA) scans, and scoliosis films. The patients received a yearly HIES score, using a diagnostic scoring system based on ascertainment of immunologic and non–immunologic disease features in which HIES diagnosis is likely with a score of 40 or above, uncertain with a score 20-40, and unlikely with a score less than 20.[4]

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TABLE I. Patient characteristics

Patient no.	Age at death (y)	Antimicrobials at time of death	Maximum HIES score	Lung cyst	Mucocutaneous candidiasis	Age at first pneumonia (y)	Age at first known fungal pneumonia	Age at first known *Pseudomonas* infection (y)	Lung resection
1	29	Trimethoprim/ sulfamethoxasole, fluconazole	82	Yes	Yes	3	NA	23	Left lower lobe at 4 y followed by left pneumectomy at 15 y
2	24	Vancomycin, meropenem, amphotericin*	71	Yes	Yes	7	*A fumigatus* and *Aspergillus niger* at 23 y	23	No
3	40	Levofloxacin, itraconazole, cefixime	87	Yes	Yes	12	*A fumigatus* at 37 y	36	No
4	24	None†	87	Yes	Yes	2	*A fumigatus* at 18 y	18	Right lower lobectomy at 23 y
5	29	Vancomycin, cefepime, amphotericin	87	Yes	Yes	<10	*A fumigatus* at 27 y	27	Right upper lobectomy at 28 y
6	32	Levofloxacin, itraconazole	68	Yes	Yes	18	*A fumigatus* at 31 y	NA	Left lower lobectomy at 31 y

*Patient 2 was on posaconazole under an investigational protocol until 1 week before her death.
†Patient 4 voluntarily discontinued her antimicrobial 1 month before her death. She had been on itraconazole, trovafloxacin, and inhaled tobramycin.

Five patients undergoing autopsy died either at the NIH or were transported to the NIH for autopsy as rapidly as possible after death. In 1 case, only slides from an autopsy performed elsewhere were available. No patient was embalmed before autopsy, and no autopsy was more than 48 hours from the time of death. All pathologic specimens were reviewed by the same pathologist (D.E.K.) and all brain specimens by the same neuropathologist (M.Q.).

RESULTS

Patient characteristics

We identified 6 female patients with HIES who died between 1998 and 2003 and had autopsies performed at the NIH (Table I). Five of the 6 women were white; 1 was African American. The age at death ranged from 24 to 40 years (mean, 29.7 years). The HIES scores of the patients ranged from 68 to 87 years (mean, 80 years), which indicates that the diagnosis of HIES was very likely in each patient. Peak IgE ranged from 12,800 to 38,572 IU/mL (mean, 19,794 IU/mL). In addition to having a history of eczema and increased serum IgE levels, all patients had histories of pneumonia (average age of first pneumonia, 8.6 years), and all had lung cysts (Fig 1). Five patients had histories of pneumonia with *Aspergillus* species, and 5 had histories of *Pseudomonas* pneumonias. As is typically observed in HIES, the fungal and *Pseudomonas* pneumonias were not the first pneumonias of the patients, as these organisms are typically superinfections of pneumatocoeles formed from previous bacterial pneumonias. The first *Aspergillus* pneumonia occurred an average of 17 years after the first bacterial pneumonia, and the first *Pseudomonas* pneumonia 19 years after, often with the 2 occurring simultaneously or in close succession. Four of the 6 patients had had pulmonary lobectomies, and 1 went on to a complete pneumectomy. Many other common features of HIES were observed among these patients, including mucocutaneous candidiasis and characteristic facial features in all 6 patients, joint hyperextensibility and scoliosis in 5 patients, and delayed dental shedding in 4 patients.

All patients except patient 4 were on antimicrobials, including an antifungal agent at the time of death (Table I). Patient 4 had discontinued her antimicrobials 1 month before death voluntarily because of her poor prognosis. Patient 2 was receiving the investigational antifungal posaconazole as part of an Institutional Review Board–approved NIAID protocol until 1 week before her death. No patients were on intravenous immunoglobulin or experimental cytokine therapy at the time of death.

Causes of death

Three patients died outside a hospital (Table II). Patient 1 had been walking on her college campus and collapsed from a massive pulmonary hemorrhage; *Pseudomonas* pneumonia was found at autopsy. Patient 3 collapsed from a massive pulmonary hemorrhage while shopping; invasive pulmonary aspergillosis was found at autopsy. Patient 6 was found dead at home; bacterial bronchopneumonia with *Aspergillus* and *Pneumocystis jiroveci* infections was found at autopsy.

The other 3 patients had more protracted hospital courses. Patient 2 had a prolonged hospitalization for a multi-organism pneumonia, including *Pseudomonas* and *Scedosporium prolificans*. Despite extensive antimicrobial

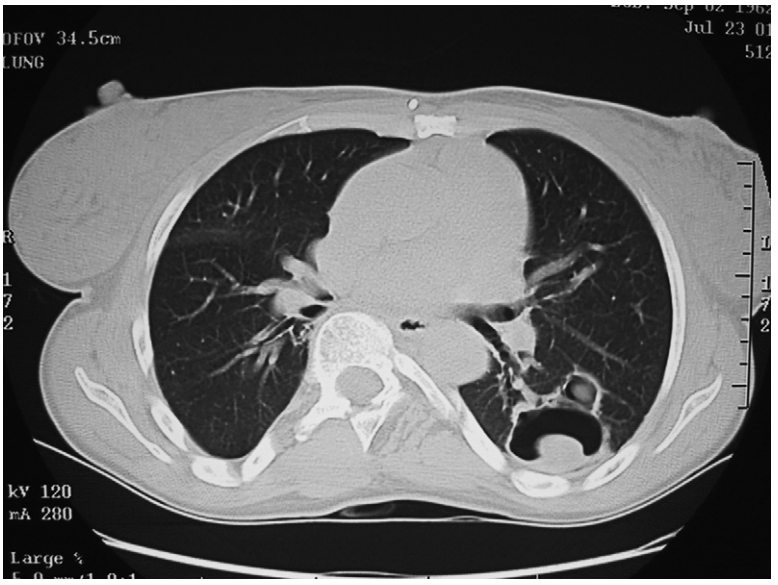

FIG 1. Chest CT of patient 1 showing pneumatocoeles characteristic of HIES, with aspergilloma present within the pneumatocoele.

therapy, the *Scedosporium* metastasized to the brain, which led to her death. Patient 4 had a progressive *Pseudomonas* and *Aspergillus* pneumonia and died of progressive respiratory failure despite extensive antimicrobial therapy. Patient 5 presented with a seizure from a left temporal hemorrhage. Her neurologic status worsened, and a left middle cerebral artery mycotic aneurysm was diagnosed. Fatal subarachnoid hemorrhage ensued. *Aspergillus fumigatus* was found in the lung and cerebral mycotic aneurysm.

Pathology

Pulmonary findings (Table II). Overall, patients with fungal disease showed evidence that infection was associated with or even began in medium-to-large–size bronchi. In several cases fungal forms, were present within intact bronchial lumena along with a significant inflammatory infiltrate. Where larger abscess cavities had formed, remnants of bronchial wall could frequently be identified. Cavities were lined by a dense inflammatory infiltrate composed mainly of lymphocytes, eosinophils, and macrophages. Little or no fibrosis was found around most cavities. Patients 3, 5, and 6 had cavitary lung disease with hyphal forms consistent with *Aspergillus* observed on Gomori methenamine silver (GMS) stain within cavities and with local vascular invasion leading to hemorrhage (Fig 2, *A-C and E*). Culture confirmed *A fumigatus* infection for patients 3 and 5. Patient 6 had cavitary lesions with hyphal forms within and invading the capsule, as well as organisms consistent with *P jiroveci* outside the cavity, with surrounding acute and chronic inflammation (Fig 2, *D*). Patient 1 had multiple pulmonary cavities and pan-lobar pneumonia with massive, diffuse hemorrhage and thrombus in a large pulmonary vessel. Stains for microorganisms were negative, but culture at autopsy grew *Pseudomonas aeruginosa*, *Candida albicans*, and alpha-hemolytic streptococcus. Patient 2 had multiple areas of consolidation and pneumonia with neutrophilic infiltrate. GMS stain showed budding hyphal elements (Fig 2, *F*), and culture at autopsy grew *S prolificans,* along with a mixture of gram-negative bacilli, gram-positive cocci, and gram-positive bacilli. Patient 4 had multiple areas of abscess formation with necrosis, neutrophil infiltrate, and intra-alveolar hemorrhage, likely from bacterial pneumonia, as well as emphysematous changes. Fungal stains were negative. Premortem sputum cultures grew *P aeruginosa* and *Candida* species; autopsy cultures grew *Klebsiella pneumoniae* and *Lactobacillus* species. Lung tissue from a previous lobectomy had shown *Aspergillus* without vascular invasion.

Central nervous system findings (Table II). Patient 1 had an area of hemorrhage within the cerebellum (1 × 2 mm) associated with focal vascular ectasia and a few mildly ectactic vessels in the hippocampus. Slightly increased numbers of mononuclear cells were observed in the leptomeninges. Patient 2 had cerebritis with areas of hemorrhage, with budding and branching hyphal elements present on GMS and periodic acid–Schiff stains, consistent with *S prolificans* (Fig 3, *A*). Patient 3 had bilateral carotid aneurysms, which had been clipped. Subarachnoid hemorrhage at the time of aneurysm presentation had led to extensive fibrosis and adhesions at the base of the brain. An area of old infarct was present in the left basal ganglia. Mild atherosclerosis was present in the circle of Willis arteries. Patient 5 had thrombosis and aneurysmal dilation of the left middle cerebral artery with invading fungal elements within the artery lumen and infiltrating the vessel wall (Fig 3, *B*). A necrotic area (4 × 4 × 3 cm) involved the left thalamus and basal ganglia, with ischemic changes in the left insular cortex. Blood clots were found in the

TABLE II. Pathologic abnormalities observed

Patient no.	Cause of death	Pathology			
		Lung	Brain	Kidney	Other
1	Sudden; pulmonary hemorrhage secondary to *P aeruginosa* pneumonia	Cavitary; multi-lobular pneumonia with diffuse hemorrhage	Focal vascular ectasia with small area of hemorrhage in cerebellum	No abnormalities	Cardiomegaly with right ventricle dilation; hepatic congestion likely from right ventricle failure; chronic hepatitis B with portal fibrosis
2	Prolonged course; multi-organism pneumonia; *S prolificans* cerebritis	Multi-lobular pneumonia with budding hyphae; culture with *Scedosporium*	Cerebritis with budding hyphae	Pyelonephritis with budding hyphae	None
3	Sudden; pulmonary hemorrhage secondary to *A fumigatus*	Cavitary with local vascular invasion by *Aspergillus*	Clipped bilateral carotid aneurysms; old areas of fibrosis from previous hemorrhage	Renal tubular injury and calcification; glomerulosclerosis; 2 angiomyolipomas	Mild coronary artery atherosclerosis
4	Progressive *Pseudomonas* and *A fumigatus* pneumonia	Multi-lobular pneumonia with intra-alveolar hemorrhage, emphysematous changes	No abnormalities	Renal tubular injury and calcification; glomerulosclerosis	Stomach and duodenal intramucosal hemorrhages
5	Multiple CNS bleeds secondary to *A fumigatus* mycotic aneurysms	Cavitary with local vascular invasion by *Aspergillus*	Left MCA thrombosis and aneurysm with infiltrating fungal elements	Renal tubular injury and calcification; glomerulosclerosis	Mild coronary artery atherosclerosis
6	Sudden; pneumonia with *Aspergillus* and PJP	Cavitary with local vascular invasion by *Aspergillus*; *PJP* outside cavity with acute/chronic inflammation	No abnormalities	Renal tubular injury and calcification	Right ventricle hypertrophy with hepatic congestion

CNS, Central nervous system; *MCA*, middle cerebral artery; *PJP*, *Pneumocystis jiroveci*.

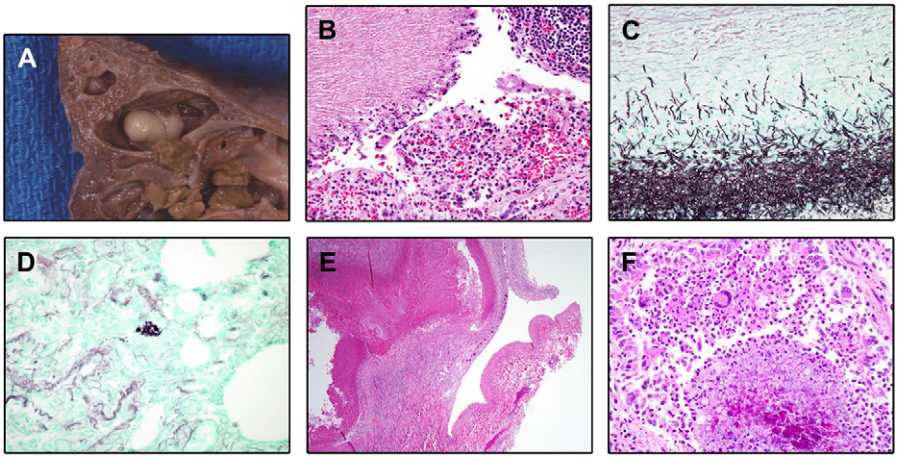

FIG 2. A, Patient 3, gross lung specimen showing pneumatoceles. **B,** Patient 6, fungal elements within bronchus. **C,** Patient 6, fungal elements within pulmonary cavity (GMS stain). **D,** Patient 6, pneumocystis adjacent to the pulmonary cavity (GMS stain). **E,** Patient 5, vessel with infected thrombus. **F,** Patient 2, fungal elements within bronchiole with granulomatous inflammation.

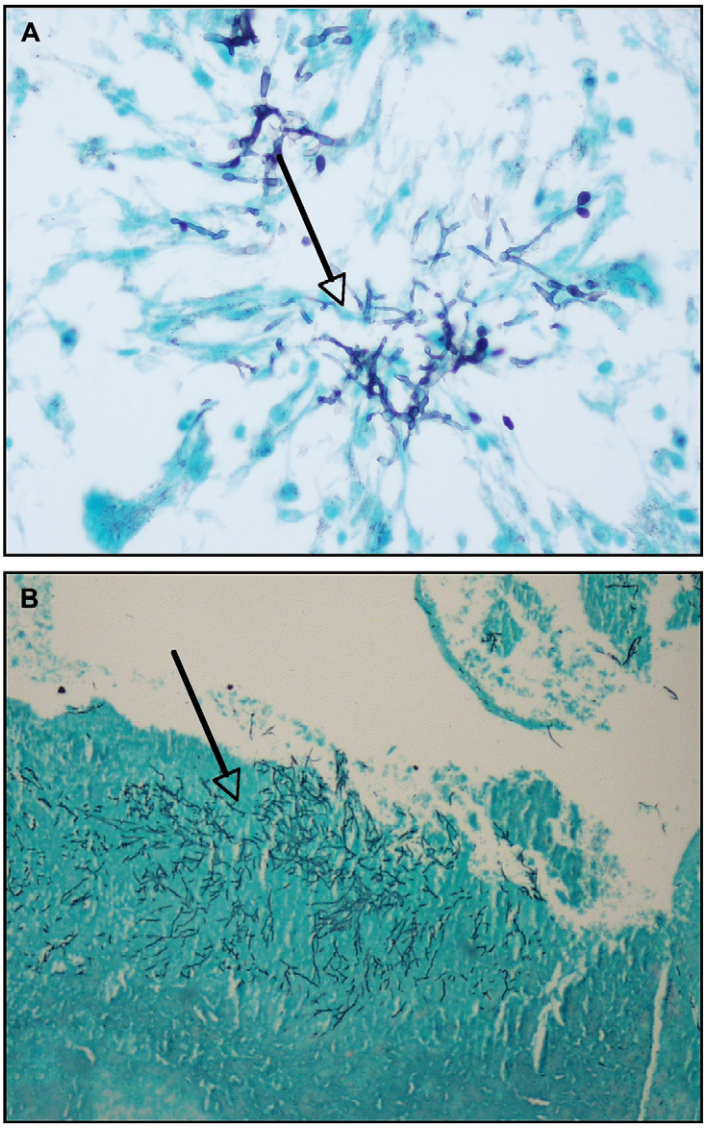

FIG 3. A, Patient 2, cerebritis with budding hyphae (GMS stain). **B,** Patient 5, left middle cerebral artery thombosis with fungal elements (GMS stain).

lateral and fourth ventricles. Patients 4 and 6 had no pathologic abnormalities of the brain identified.

Cardiovascular findings. Patients 1 and 6 had right-ventricular abnormalities likely secondary to chronic lung disease. Patient 1 had cardiomegaly (480*g*) and right ventricular dilation, and patient 6 had right ventricular hypertrophy with mild interstitial fibrosis. Patients 2-5 had no significant cardiac abnormalities. Mild atherosclerosis was present in patients 3 and 5, but no atherosclerosis was present in patients 1, 2, and 4. Arterial examination for atherosclerosis was not performed for patient 6, as only selected slides were obtained from the institution where the patient expired.

Hepatic findings. Patients 1 and 4 had evidence of hepatic congestion with sinusoidal dilation, likely caused by right ventricular failure. In addition, patient 1, known to have had chronic hepatitis B, had portal fibrotic expansion consistent with this infection.

Gastrointestinal findings. Patient 4 had intramucosal hemorrhages in the stomach and duodenum, which may have been secondary to chronic exogenous steroid therapy for chronic lung disease.

Renal findings. Patient 2 had fungal dissemination to the kidneys from her primary pneumonia with acute pyelonephritis. Patients 3-6 had evidence of renal tubular injury and calcification most consistent with amphotericin B toxicity. Patients 3-5 had glomerulosclerosis, which was fairly extensive for patients 4 and 5. Patient 3 had 2 small angiomyolipomas in the right kidney (Fig 4). These tumors were composed of a mixture of fat cells and plump

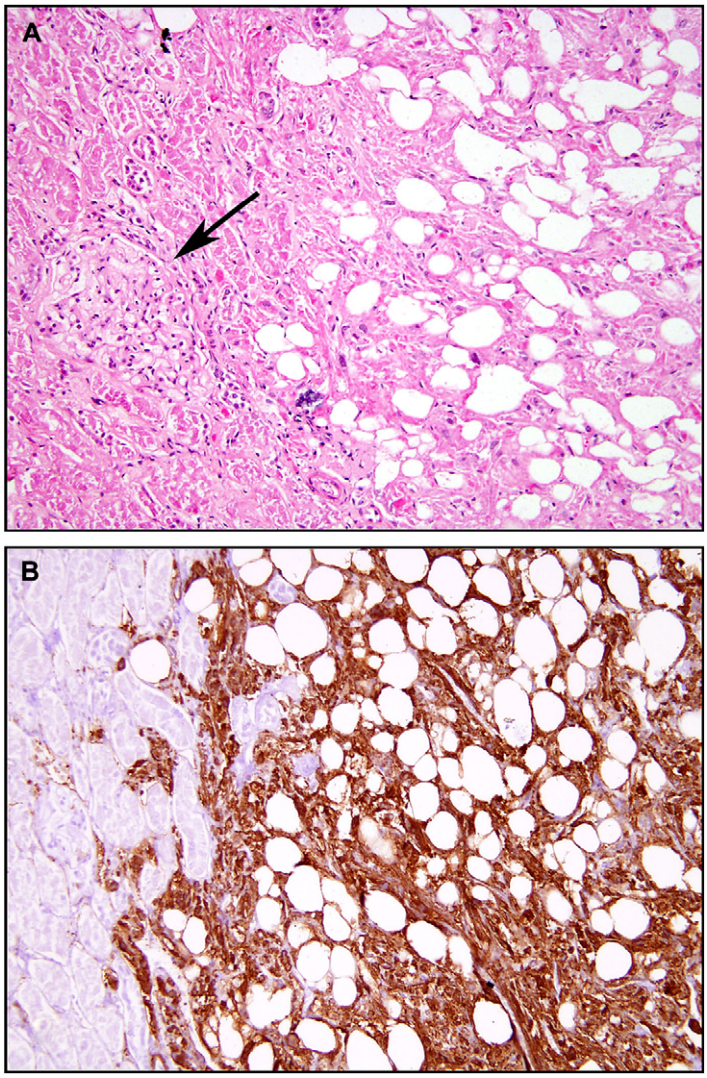

FIG 4. Angiomyolipoma found in renal cortex of patient 3. **A,** Interface between tumor and normal kidney. A normal glomerulus is indicated by the *arrow*. The tumor is composed of fats and eosinophilic spindle cells. Trapped tubules are present within the tumor (hematoxylin and eosin stain, ×200). **B,** Immunohistochemical staining for smooth muscle actin, which is strongly positive in the spindle cell component of the tumor but negative in renal tubular cells and glomeruli (anti–smooth muscle actin stain, ×200).

spindled myocytes. By immunohistochemical staining, the spindled cells were strongly positive for smooth muscle actin and focally positive for Melan-A.

Other. Patients 1, 3, and 5 had ovarian cysts. Patient 3 had multiple uterine leiomyomata. Patient 4 had breast fibrocystic changes. No gross abnormalities of bone architecture were noted for patients 1-5 (specimens were not available for patient 6).

DISCUSSION

Patients with HIES often develop pulmonary insufficiency after many years of recurrent pneumonias with cyst formation. Similar to other immunodeficiency syndromes, patients with HIES are also at increased risk of lymphoma.[5] Although reports of death from infection and lymphoma exist, no systematic reviews of causes of death or pathologic findings at autopsy in these patients have been published.

All patients we report died from either infection directly or a complication related to infection, and all had pathologic evidence of active pneumonia at the time of death. Without prophylactic antibiotics, infections in HIES start from a very young age, and the pulmonary infections lead to bronchiectasis and characteristic pneumatocoeles. Typical organisms that cause pneumonia in intact lung are *S aureus, Haemophilus influenzae*, and *Streptococcus pneumoniae*. The pneumatocoeles formed secondary to bacterial pneumonias may subsequently become colonized and infected with fungi and gram-negative bacteria, which are the infections associated

with mortality in our series. Mortality from these organisms, including fungal dissemination, indicates that these organisms are not merely colonizing the pulmonary cavities but are pathogenic and need to be aggressively treated.

Limited literature exists on surgical or autopsy pathology from patients with HIES. In 1 series, cystic lung tissue from 4 patients (from autopsy or surgical specimens) with fibrotic walls and chronic inflammation was described, with bronchial communication observed in at least 2 cases.[6] *Aspergillus* hyphae were observed in 2 cases, but vascular invasion was not described. A pneumonectomy specimen showed a cyst with chronic inflammation, necrosis, and *A fumigatus*.[7] Although arteritis with thrombus was observed next to the cyst, fungal invasion was not observed. The only reports of extrapulmonary pathology are of a bone marrow without plasma cells and of a lymph node with normal lineage but reduced numbers of plasma cells.[8]

This autopsy series found that all patients died directly or indirectly of lung infection. Lung abnormalities predominated with cystic lesions associated with chronic inflammation. Local fungal vascular invasion was observed; dissemination of fungi to the brain occurred in 2 patients and to the kidney in 1 patient.

Most patients had abnormal renal histologic findings, including evidence of presumed amphotericin B toxicity, with renal tubular damage and calcium deposition. This result seems to occur from a direct amphotericin B effect on the renal tubules, an amphotericin-related decrease in renal blood flow, and a consequent decreased glomerular filtration rate.[9] Glomerular abnormalities have been observed after amphotericin therapy but are not as frequent or marked as tubular changes.[10,11] Glomerulosclerosis in 3 of our patients may have been the result of an abnormality intrinsic to HIES, which may relate to other connective tissue abnormalities of the syndrome. Kidney disease is not typically associated with HIES, but perhaps, as patients with HIES live longer with improved antimicrobial therapy, more renal dysfunction and abnormalities will become apparent. The angiomyolipomas found in the kidney of 1 patient may be related to HIES, as angiomyolipomas are uncommon incidental findings, which occur as incidental findings at a rate of .02% to .29% of the population. They are typically associated with tuberous sclerosis and lymphangioleiomyomatosis (LAM).[12] It is interesting to note that LAM, a rare predominantly interstitial lung disease of women, is characterized by cystic degeneration of normal lung[13] and, therefore, may share some pathogenic similarities with HIES. Tuberous sclerosis has been linked to 2 tumor suppressor genes, *TSC1* and *TSC2*, on chromosomes 9q34 and 16p13, respectively, and LAM and sporadic angiomyolipomas have been associated with somatic mutations and loss of heterozygosity at *TSC2*.[12] Although we had only 1 patient with both HIES and renal angiomyolipomas, continued investigation may be warranted.

No patients in our study were found to have malignancies during autopsy. Lymphoma occurs at an increased rate in HIES, which suggests that, in addition to the infections we report here, lymphoma may be a significant cause of death in HIES. In a review summarizing 13 patients with HIES and lymphoma, 7 of 11 with reported outcome died, with at least 5 secondary to the lymphoma.[5] The increased mortality is not surprising, as lymphoma tends to present in this population at an advanced stage with extranodal involvement.

Although HIES is thought to occur in equal incidence in men and women, all patients in this series were women. In part, this outcome may be from referral bias, as we have not had access to autopsy specimens for all deceased patients. In a previous report of 30 patients, 20 were women and 10 were men; of the 6 reported fatalities, only 1 was male.[2] Although women have not been reported to have a more severe disease course, more investigation is necessary to determine whether any differences exist in the severity of disease and causes of death between men and women.

This autopsy series highlights the important roles that gram-negative bacteria and fungi play in adults with HIES and pneumatocoeles. HIES is typically characterized by recurrent bacterial infections from a young age with *S aureus* and *H influenzae*. However, we found *Pseudomonas* and/or fungi as immediate causes of death. The proven success of anti-staphylococcal prophylaxis in preventing boils and pneumonias early in the course of HIES suggests that it may also be advantageous to provide aggressive antifungal and gram-negative prophylaxis to adults with HIES, especially those with pneumatocoeles.

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