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Surgical and Medical Management of Sinus Mucosal and Systemic Mycotoxicosis

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Abstract

Two women, ages 53 and 26, exposed to fungi in their water-damaged homes, presented with sinus and neurological symptoms. Sinus CT scans revealed bilateral fungal ethmoid sinusitis in both patients. The older patient also had a brain MRI that indicated probable microvascular inflammation in the grey and white matter junction. After maximal medical therapy, with no improvement in sinus or neurological symptoms, endoscopic sinusotomies were performed on both patients to remove polypoid sinus mucosa and possible mucosal mycotoxins. Samples of the extracted mucosa were then cultured on SDA agar plates. The cultured tissue was also tested for mycotoxins. The tissue from the 52-year-old woman was positive for mycotoxins as follows: Ochratoxin A (> 10 ppb), Macrocyclic trichothecenes (> 10 ppb), and Gliotoxin (> 10 ppb). The 26-year-old woman's extracted and cultured ethmoid mucosa was also positive for mycotoxins as follows: Gliotoxin (0.35 ppb). Gliotoxin, which was present in both tissue samples, is a mycotoxin consistent with Aspergillosis of the ethmoid sinuses.

These findings are discussed with respect to sinus mucosal fungal mycotoxin presence, and translocation of toxins and fungal spores via accepted avenues, as well as through the olfactory nerve into the hypothalamus/pituitary axis. These findings give laboratory and case study proof of the following conjecture: Toxic mold exposure that results in chronic sinusitis and other systemic symptoms, and which fails to respond to maximum medical treatment, may require functional endoscopic sinus surgery (FESS) to remove sinus mucosal mycotoxins, as well as intraoperative Amphotericin-B irrigation to improve systemic symptoms.

Keywords: Sinus Mucosal; Systemic Mycotoxicosis; Mycotoxin

Introduction

Exposure to conditions of water-damaged indoor environments results in fungal infections of the paranasal sinuses with involvement of the hypothalamus/pituitary axis and depletion of growth hormone [1–4]. In a case study of immunocompetent patients, invasive cerebral aspergillosis involved three types: Type 1 involved orbital and cranial based Aspergillosis; Type 2 was intracerebral Aspergillosis that may respond to orally administered Itraconozole; and Type 3 was intermediate to Types 1 and 2 [5]. Fungal invasion also occurred in the orbits [6,7], basilar artery, cerebral aneurysm [8,9], otitis and meningeal extension [10]. In addition, fungi have been identified in the brains of individuals with Alzheimer's disease and amyotrophic lateral sclerosis [11,12]. While Candida species have been implicated in their role in multiples sclerosis [13–15], we have also reported the presence of mycotoxins in patients with fungal sinusitis. For example, nasal mucous from the father and daughter with fungal sinusitis were positive for mycotoxins as follows: Father had aflatoxins at 11.2 ppb and trichothecenes at 7.7 ppb, while the daughter had ochratoxin at 3.8 ppb and trichothecenes at 4.68 ppb [4]. In another case study, 0.28 ppb trichothecenes were detected in a brown halo expanding from sinus mucosa on the SDA agar from another patient with fungal sinusitis [16]. In this communication, two more female patients with chronic fungal sinusitis and neurological symptoms are presented with mycotoxins present in surgical specimens removed from the diseased sinuses. This communication will demonstrate that by identifying and surgically removing the mycotoxic fungus from the patients' sinuses and eliminating the source of the mold exposure (ex. no longer living in the mold-infested home), sinus, neurological and other systemic symptoms improve significantly.

Materials and Method

Brief Review of Medical Records

Patient 1: The first patient is a 53-year-old woman with a history of mold exposure to fungi in a water-damaged building, while at her job at a Pregnancy Resource Center, Lawrenceville, GA. She reported that hammering on a mold filled wall in 2012, resulted in burning nostrils and trigeminal pain by night fall. The medical records from her treating physician are summarized as follows: An MRI of the brain without contrasts showed a 3 cm cyst in the right maxillary sinus and scattered punctuate areas of high signal in the subcortical white matter bilaterally that demonstrated white matter lesions, consistent with prominent microvascular disease for her age (Figure 1,2).

Immune tests showed her IgG subclasses II and III were low. Her IgG subclass I was 582 mg/dl (normal 382–929 mg/dl), IgG subclass II was low at 190 mg/dl (normal 241–700 mg/dl), IgG subclass III was 14 (normal 22–78 mg/dl), and IgG subclass IV was 16 (normal 4–86). Total IGG was 913 (normal 694–1618 mg/dl), which demonstrates some immune suppression. Most patients who have mycotoxicosis symptoms have some low IgG subclasses. The specific IgG subclass deficiency varies [1].

Medical therapy included: Moving into her mold-free beach house, sinus irrigation twice a day with normal saline, Amphotericin-B nebulization twice a day (Amphotericin 3 mg in 30 ml sterile water with 0.25 mg Dexamethasone), oxygen (100% at 10 L/min for 2 hr qd with regular face mask), Acetyl Glutathione (300 mg po bid), Opticleanse GHI liver detoxification (1 scoop in 6 oz water bid), methylcobalamin B12 (1000 mcg) L-methylfolate (800 mcg po qd–for those with MTHFR mutations), Sinus Defense (9 sprays sublingual bid--transfer factor to support immunity to fungi and bacteria in sinusitis by Microbalance Health Products), and Intramax liquid multivitamins (1 oz qd--415+ vitamins, minerals amino acids, minerals, vegetables, probiotics, digestive enzymes, all bound to organic carbon for intracellular release and detoxification). In addition, after completing Fluconazole (100 mg QD for 14 days), she switched to Itraconazole (100 mg bid pc) for 1–2 months or longer, depending on symptom resolution. Patient was compliant with maximum medical therapy, and did not experience much improvement.

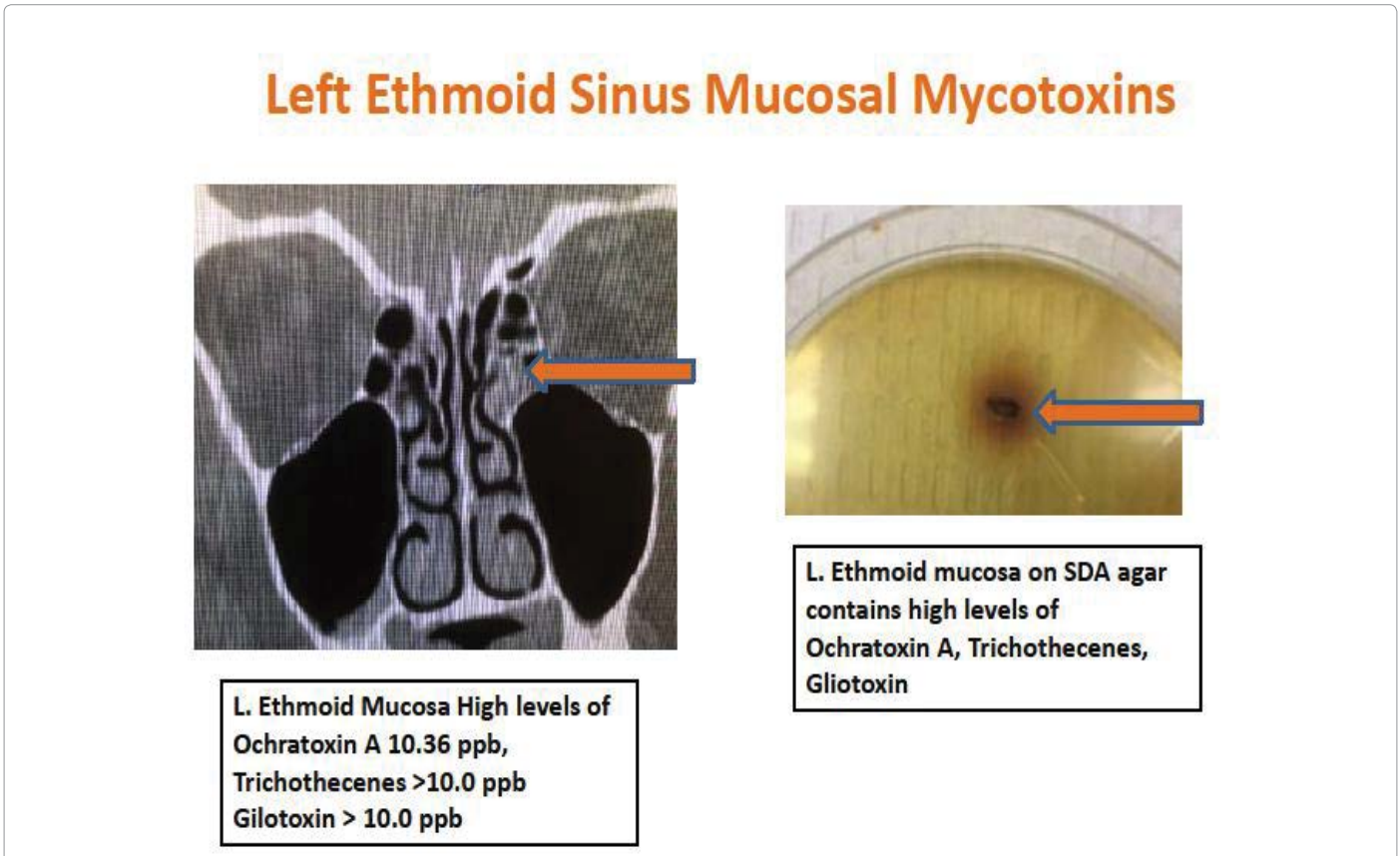

Figure 1: Sinus CT scan of patient 1 showing bilateral maxillary sinus mucosal thickening with right > left. Bilateral ethmoid disease, left > right. The left ethmoid polyploid opacification is the mucosa on SDA agar plate on the right from which Ochratoxin, Trichothecenes and Gliotoxin derivative were identified. (See Table 5).

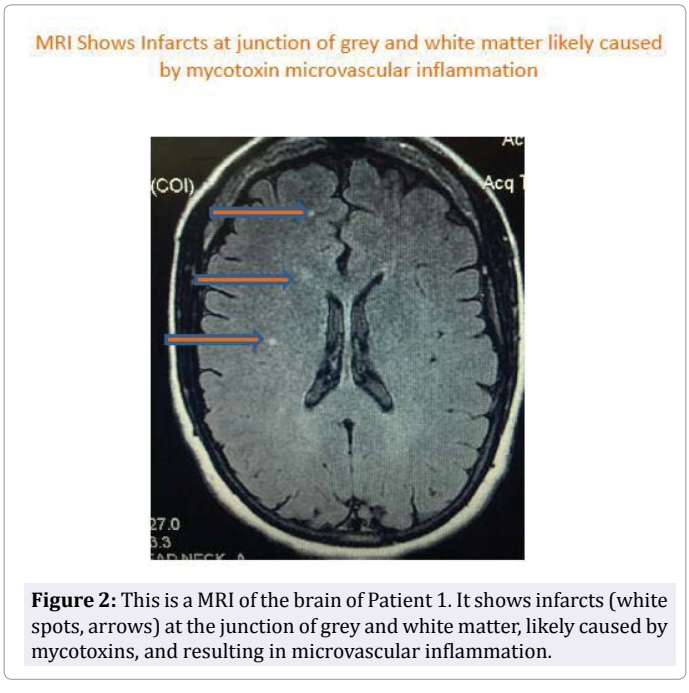

Figure 2: This is a MRI of the brain of Patient 1. It shows infarcts (white spots, arrows) at the junction of grey and white matter, likely caused by mycotoxins, and resulting in microvascular inflammation.

The ethmoid sinuses had polypoid mucosa, which were thought to be harboring fungus and mycotoxins. Therefore, she had endoscopic sinus surgery with Amphotericin-B irrigation of all the sinuses. The excised sinus mucosa revealed high levels of three mycotoxins: Ochratoxin A (> 10.3 ppb), Macrocyclic trichothecenes (> 20.0 ppb) and Gliotoxin Derivative (> 10.0 ppb) (Table 1).

Sinus Mycotoxins	Patient 1	Patient 2
Ochratoxin A	10.3 ppb	0.43 ppb
Aflatoxins	N.T.	0.22 ppb
Trichothecenes	>10.0 ppb	0.01ppb
Gliotoxin Derivative	>10.0 ppb	0.35 ppb

Table 1: This table summarizes the mycotoxins by Real Time Laboratories present in the tissue samples taken from the sinuses of Patients 1 and 2. (N.T. Not Tested. Limit of Detection: Ochratoxin (2.0 ppb); Aflatoxins (1.0 ppb) Macrocyclic Trichothecenes (0.2 ppb), Gliotoxin Derivative (0.3 ppb)).

Post operatively, she had marked improvement. Her cognitive function went from 1–2 to 8–9, with 10 being normal. Her energy level went from 1–2 to 6–7, with 10 normal. The remainder of her symptoms (see above) also resolved.

Patient 2: This patient is a 26-year-old woman with a history of toxic mold exposure, due to a flood in her apartment. She had a sinus infection for two and a half months, as well as a deviated nasal septum, nasal airway obstruction, ringing and fullness in her ears, dizziness, sinus pressure, frequent yeast infections, shortness of breath, abdominal pain, constipation, bloating, gas, weakness, blurred vision, insomnia, laryngitis, anxiety, depression, irritability, dizziness, skin rashes, urticaria, and vocal cord nodules. Her symptoms improved when she was away from the apartment. She began having UTI's and yeast infections six months after moving into the moldy apartment. She began to recover after she moved out of the apartment.

Medical therapy included: Normal saline nose washes (4

oz each nostril bid), nasal Amphotericin-B nebulization (3 ml bid--Amphotericin 3 mg in 30 ml sterile water with 0.25 mg Dexamethasone), Fluconazole (100 mg po bid) for 2–4 weeks. After completing Fluconazole, she started Itraconozole (100 mg po bid pc),VSL # 3 flora (900 billion Probiotic units bid), Complete Thymic formula (2–3 bid pc - a multivitamin with thymus by Logos Nutritional), Acetyl Glutathione (300 mg bid), UltraClear Plus liver detox phase I and II detoxification pathways by Metagenics (start 1 scoop in 6 oz water bid, work up to 2 scoops bid), oxygen (100% at 8–10 liters per min. with regular face mask 1 hr bid or 2 hrs qd), Chlorella (8 tablets bid to bind neurotoxins and heavy metals), and Sinus Defense (9 sprays sublingual bid (transfer factor to support immunity to fungi and bacteria in sinusitis by Microbalance Health Products), and methyl B12 (1000 mcg and 5- methyl tetrahydrofolic acid 400 mcg 1 qd for support in MTHFR mutations, which decreases ability to excrete toxins).

Because she had positive urinary mycotoxins and was treatment compliant and not improving, she had endoscopic sinus surgery to remove the diseased mucosa, which contained mycotoxins, followed by intraoperative irrigation with Amphotericin-B. Her excised ethmoid sinus mucosa was positive for 0.35 ppb Gliotoxin (Table 1). Her symptoms markedly improved after surgery, and neurological issues, ear ringing, sinus pain, and dizziness subsided. Her energy score went from a 3–4 to 7, with 10 being normal. Her oxygen saturation went from 96–98%. Her cognitive function went from 3–4 to 8–9 out of 10.

Fungal Contamination of Home of Patient 1

The home of patient 1 was investigated for water intrusion and fungal contamination by Air Allergen Mold Testing, Inc., Stone-Mountain Road, Stone Mountain, GA. Airborne spore counts were collected with Allergenco D Pos-Tack Cassettes (EMLab P & K). The results are summarized in Table 2.

Fungal Cultures of the Home and Apartment of Both Patients

Both patients were instructed to collect various surface samples in their individual homes, using SDA Agar plates. To collect the samples, they were instructed to invert the SDA Agar plates on a surface, tapping the plates 3 times against the surface to dislodge and collect any mold spores. The plate's cover lid was then replaced, and the plates sealed by cellophane tape. The samples were then shipped to Immunolytics, Albuquerque N.M., via UPS in sterile zip lock bags. Immunolytics cultured the samples at room temperature, until fungal growth appeared. The colonies were identified to the genus level. The results are summarized in Tables 2–4.

Master Bedroom	CFU/g	Basement	CFU/g
Asp. brasilensis/niger	217	*Chaet. globosum*	4,128
Asp. versicolor	217	*Asp. ustus*	459
Chaet, globosum	652	*Mucor sp*	459
Eurot. Amstelodami	217	*Penicillium sp.*	8,716
Cladosporium sp.	3,696	*Asp. ochraceus*	459
Mucor sp.	2,174	*Eurot. Amstelodami*	1,375
Penicillium sp.	1,522	*Asp. versicolor*	1,376
Rhodotorula sp.	217	*Cladosporium sp.*	4,128
Trichoderma sp.	217		
Yeast	1,957		

Table 2: This table summarizes the fungi identified in the dust samples obtained from the master bedroom and the basement of Patient 1. The CFU/g of dust is also listed.

Sinus Examinations

Sinus endoscopy was performed on each patient with an Olympus ENFP fiber optic scope with Storz HD video camera and a Sony video printer.

Area Tested	Microbe I.D.	Number of Colonies
Bedroom Chair	*Alternaria*	2
	Bacteria	TNTC
	Candida	TNTC
	Cladosporium	3
	Geotrichum	4
	Nocardia	5
	Rhodotorula	9
Pillow and Bedding	*Bacteria*	2
	Candida	TNTC
	Cladosporium	1
	Geotrichum	1
	Nocardia	5
	Rhodotorula	2
Guest Bedroom – Air	*Microsporium*	7
Master Bedroom – Air	*Candia*	1
	Microsporium	4
Nasal Mucosa	*Bacteria*	3
	Candida	25
	Cladosporium	11
	Epicoccum	1
	Penicillium	1

Table 3: This table summarizes the results of fungal cultures from various areas of the home and nasal secretions of Patient 1, identified by Immunolytics Lab on SDA agar plates. (TNTC: Too Numerous to Count).

Areas Tested	Microbe I.D.	Number of Colonies
HVAC Duct	*Cladosporium*	TNTC
	Microsporium	TNTC
	Rhodotorula	4
Bathroom Wall	*Cladosporium*	3
	Mucor	TNTC
	Penicillium	TNTC
Office Wall	*Rhizopus*	TNTC
Bedroom	*Candida*	20
	Geotrichium	4
	Microsporium	1
Living Room – Air	*Cladosporium*	1
	Penicillium	1
	Rhizopus	TNTC
Spare Room	*Bacteria*	2
	Candida	1
	Cladosporium	2
	Microsporium	1
	Rhizopus	TNTC
Couch	*Alternaria*	1
	Aspergillus	4
	Candia	32
	Cladosporium	2
	Fusarium	1
	Microsporium	4
	Penicillium	7
Mattress	*Bacteria*	6
	Candida	6
	Cladosporium	1
	Rhodotorula	1

Table 4: This table summarizes the fungal growth on SDA agar plates identified by Immunolytics from various areas of the apartment of Patient 2. (TNTC: To Numerous to Count).

Sinus Mycotoxins

The tissues taken from the sinuses of the two patients during surgery were transferred to SDA malt-extract agar plates and cultured at room temperature for five days. No fungal colonies were visible. The plates were then sent to RealTime Laboratories by overnight UPS. RealTime Laboratories tested the sinus tissue samples for the presence of mycotoxins--Ochratoxin A, Aflatoxins and Macrocyclic Trichothecenes as previously published [16–20]. The presence of gliotoxin derivative was identified by detecting the stable metabolite bis (methylthio) gliotoxin [19,20]. The results are summarized in Table 1.

Results

Fungal Contamination of each Residence

The results of fungal testing of residents of both patients are summarized in Tables 2–4.

Patient 1: The home of patient 1 was investigated for water intrusion and fungal contamination (Table 2). The SDA agar plates were used to identify types of fungi present in the house. (Table 3)

Patient 2: The fungi identified by Immunolytics Lab that grew on the SDA agar plates are presented in Table 4. The HVAC duct was heavily contaminated with Cladosporium and Microsporium at too numerous to count (TNTC).

Symptoms of the Patients

The symptoms of mold exposure the two patients are summarized in Table 1. The two patients had similar symptoms, which included chronic fatigue, nasal and sinus congestion, GERD and CNS symptoms of cognitive decline, depression, irritability, and anxiety. All of these symptoms of mold exposure have been published in other case studies [1–4,18,24,25].

Sinus CT Scans

Patient 1: The CT scan revealed thickening in the left ethmoid sinus at the orbit with hyper-density on the medial surface, which may indicate a fungus ball, and there was mucosal thickening in the floor of the maxillary sinus (Figure 1).

Patient 2: Sinus CT scan of the right ethmoid sinus of patient 2 shows polypoid mucosa and a septal spur into the left middle meatus (Figure 3).

Discussion

Clinically, endoscopic sinus surgery has an important role in the treatment of patients with mycotoxicosis when either they have significant sinus disease shown on CT scans, or when they have minimal mucosa disease shown on sinus CT scans and have little or no symptom improvement, even when on maximum medical therapy, as shown in the above two cases. If there is no improvement on maximum therapy even in minimal mucosal disease, endoscopic sinus surgery can be used to remove mycotoxins from the sinus mucosa, intra-operative sinus irrigation with Amphotericin-B can remove fungal spores, and post operative antifungal irrigation can then reach all of the sinuses to maintain fungal and mycotoxin-free mucosa. This can only work when the patient is in a safe, mold-free environment. The clinical improvement after endoscopic sinus surgery can be dramatic and warrants consideration for patients with a positive mold exposure history, and who present with multiple systemic symptoms.

Nine types of biocontaminants from microbial growth are present in water-damaged indoor environments, as follows: 1) Indicator fungi, 2) Gram negative and positive bacteria, 3) microbial nano-sized and larger particulates, 4) mycotoxins, 5)

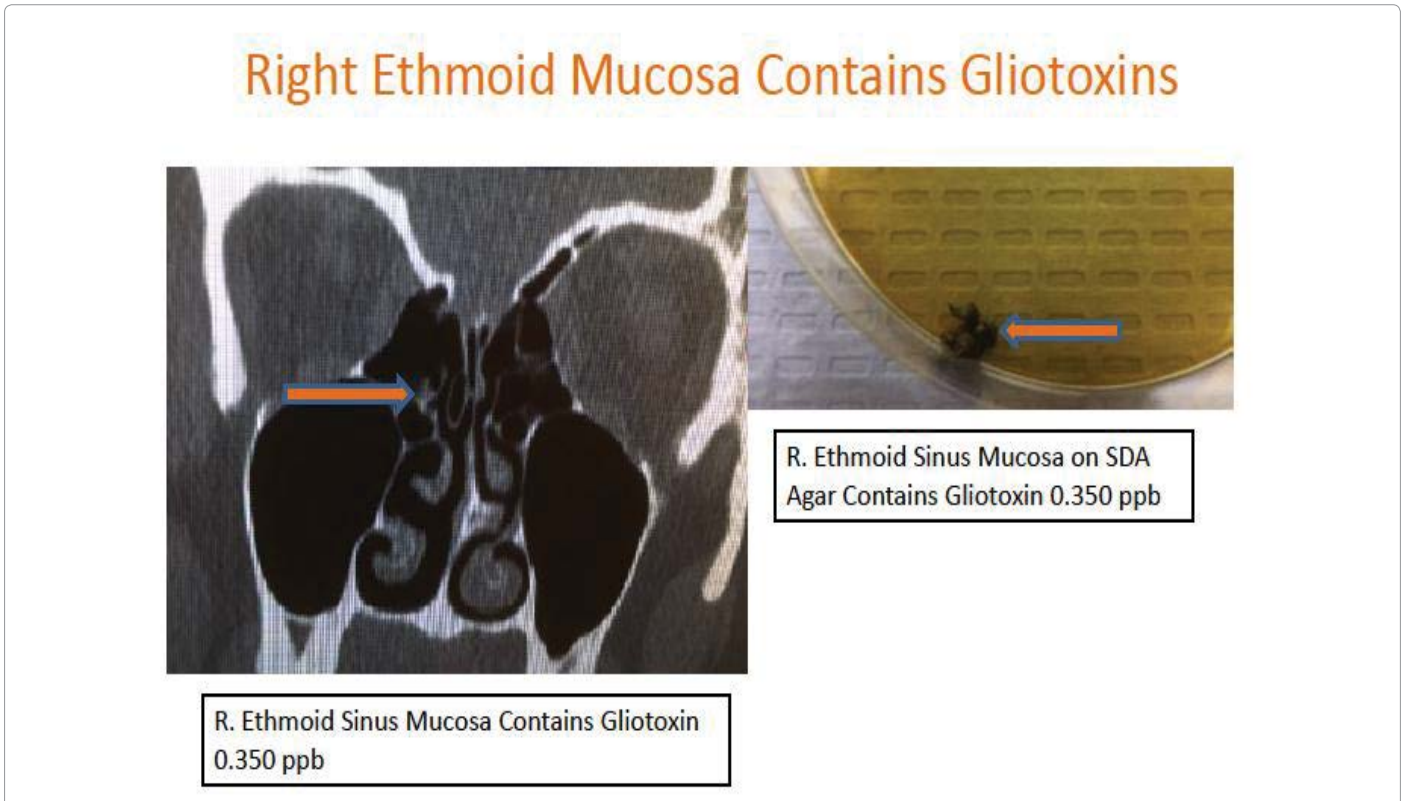

Figure 3: Sinus CT scan of patient 2 of the right ethmoid sinus showing polypoid mucosa and a septal spur into the left middle meatus. The ethmoid mucosa was excised and placed on an SDA agar plate. Gliotoxin derivative was identified in the mucosal tissue at 0.35 ppb (See Table 5).

Patient 1 – 52 yrs	Patient 2 – 26 yrs
Metallic taste, paresthesia of arms, legs, and cheek area of face, nasal burning, congestion of nasal cavity and sinuses, cognitive and memory decline, fatigue, inability to do math in her head, prolonged word search in conversation, muscle fasciculations. She felt better while away from the mold-infested home, but would become ill again upon returning. The patient rated her cognitive function at 1-2, with normal being 10, and rated her energy at 5 out of 10.	Nasal obstruction and congestion, ringing in ears, dizziness, sinus pressure, shortness of breath, bad breath, sinus infection, blurred vision, leaky gut, irritability, depression, anxiety, skin rashes, abdominal pain, fatigue, cognitive decline and GERD. The patient rated her cognitive function at 3-4, with normal at 10, and her energy level at 3-4, with normal at 10.

Table 5: This table summarizes the symptoms of the two patients.

VOCS (microbial and non microbial), 6) Allergens, 7) Endotoxins (LPS) and bacterial exotoxins, 8) Galactomannans, and 9) 1,3-beta D-Glucans. These contaminants either singularly or in combination, lead to adverse health effects in occupants [1–28]. Thus, the symptoms of the two patients listed in Table 5 are consistent with the published literature and, in particular, their symptoms of neurocognitive deficits and chronic fatigue [16,18,25,29-36].

Both patients were exposed to a variety of fungi in their water-damaged indoor environments, which included Aspergillus species (Tables 2,4). As a result, they both developed bilateral fungal ethmoid sinusitis. Mycotoxins were detected in mucosal tissue samples from the affected sinuses that included Ochratoxin A, Macrocyclic Trichothecenes and Gliotoxin Derivative in Patient 1 and trace amounts of Ochratoxin A, Aflatoxins, and Macrocyclic Trichothecenes in Patient 2. The Gliotoxin derivative was positive (Table 1). The Gliotoxin Derivative detected in their sinus mucosa was (bis) methylthio-gliotoxin, which is a stable metabolite of Gliotoxin, and represents a marker for Aspergillosis [19,20]. *Aspergillus flavus, fumigatus, niger*, and *terreus* were recovered from tissue samples of patients with aspergillosis at a tertiary-cancer center [37]. Further investigation of experimental mouse aspergillosis gliotoxin was measured in lungs (3,976 ± 1,662 ng/g) and sera (36.5 ± 30.25 ng/ml) of the infected mice. In addition, gliotoxin was detected in the sera and lungs of patients with aspergillosis, ranging from 65 to 785 ng/ml [38]. Thus, these observations show that Aspergillus spp. produce gliotoxin in the cases of colonization/infection, and should be tested in body fluids of patients [37,38].

Gliotoxin Derivative was identified in the sinus tissues of both patients, which indicates colonization and or infection by *Aspergillus spp*. However, fungus growth did not occur on the SDA agar plates. The absence of growth probably resulted from the irrigation of the nasal cavity with Amphotericin-B. However, if *Aspergillus spp*. was not the cause of the sinusitis, other explanations for the presence of Gliotoxin Derivative are known. Activity in the indoor environment, such as air currents associated with ventilation, causes the fractionation and the release of hyphal fungal fragments, ranging from nano particulates (0.03–0.3 microns) to larger [39,40]. The fungal fragments in homes are in greater concentrations than are spore counts. For example, the F/S ratio (Fragment number/spore) was shown to be 10^3 and 10^6, for the fragment sizes of 0.3 and 0.03 µm, respectively. These results indicate that the actual contribution of fungal fragments to the overall exposure may be very high, even much greater than that estimated in earlier laboratory-based studies, i.e. 500 times greater [21]. The aerodynamics of fungal fragments has a 230-250 or higher respiratory deposition in adults than fungal spores, while fungal fragment respiratory deposition in infants is 4–5 times greater, than in adults. These fragments have been shown to contain mycotoxins, endotoxins, 1-3-beta D-glucans, and antigens, and should be counted in exposure assessments (9,21-25,32-34,41). The other aspect of assessment regarding the health effects of ultra-fine particulates at or at less than one micron is their translocation after inhalation. The two major sites for the translocation of ultra-fine particulates regarding toxicology are the olfactory nerve, alveolar surfactants, and to a lesser extent, the Trigeminal nerve V [42]. Several papers have been published regarding the translocation of nano- and ultra-fine particles and their adverse effects, leading to neuroinflammation, disruption of the blood brain barrier, immunodysregulation, chronic pro-inflammatory facts, reactive oxygen species, and human health; it is recommended that readers review this research to come to an understanding of translocation via the alveolar surfactants into the systemic circulation and transportation of fine particulates via the olfactory nerve into the hypothalamic/pituitary axis [41–48]. Perhaps, the medical profession will come to a better understanding of why knowledge of the nasal and sinus mucosa and the role of alveolar surfactants is important with respect to human illness from all sources of ultra-fine particulate inhalation, be it indoors or outdoors.

In this study, patient 1 had normal total IgG but low IgG subclasses II and III. This is common with mycotoxicosis. It is also common in animals that eat fungal-contaminated food. This may be why many patients with toxic mold exposure have secondary infections such as Lyme's, Epstein Barr virus, CMV, and Herpes. It also may be why secondary infections improve when patients get into a safe environment and remove the fungus and mycotoxins from their body and sinuses. Gliotoxin is immunosuppressive by various mechanisms such as apoptosis of lymphoid tissues and monocytes [49,50], phagocytosis by altering signaling pathways of human neutrophils [51], and suppression of both innate and adaptive immune functions [52].

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