Abstract

Fungal sinus disease represents a spectrum of five different clinico-pathological entities, each linked by a common process of sinonasal inflammation secondary to fungi. Fungal sinus infection can be classified as invasive or non-invasive. The diagnosis is usually made by a combination of CT, histology and mycology features. Each type of fungal sinus infection has an individual clinical presentation, prognosis and options for treatment. Invasive infection typically occurs in an immunocompromised host and is characterised by histological destruction of tissue. Mortality rates remain high, and early detection and treatment are vital. Non-invasive fungal infections are classically more indolent and patients are usually treated for extended periods as chronic sinusitis before the condition is recognised.

Keywords
Sinusitis; fungal; classification; management

Background
Fungal sinus disease (FSD) represents a spectrum of five different clinico-pathological entities, each linked by a common process of sinonasal inflammation secondary to fungi. Although fungal infection of the sinuses was first reported in the medical literature by Mackenzie in 1893, over the last century there has been little consensus on classifying the various forms of FSD, leading to confusion with diagnosis, prognosis and treatment outcomes. FSD is estimated to affect 10% of all patients requiring surgery of the nose and sinuses and incidence appears to be increasing. This increase is probably due to a combination of factors including greater awareness of fungal sinus infections, a growing population of immunocompromised patients and recent advances in mycological, histological and radiological techniques for diagnosis.

Classification
In earlier literature, cases were generically labelled as ‘aspergillosis’ or ‘mycosis’, and often lacked the relevant histopathological data now necessary for reaching an accurate diagnosis. Over the last fifteen years, specific diagnostic criteria have gradually evolved. In 1997 deShazo et al classified patients with FSD into invasive and non-invasive categories, determined by evidence of mucosal invasion on tissue histology and a radiological diagnosis of sinusitis (Fig 1).

This review will focus on the clinical presentation, diagnostic features and treatment of each of these disease subtypes.
Identification of fungi

Several stains can be used to detect fungi in clinical specimens. Initially a haematoxylin and eosin (H&E) stain is usually performed to demonstrate the general pattern of inflammation, which in conjunction with the clinical history, is key to forming a list of differential diagnoses. Occasionally it also allows for the detection of some fungi, especially aspergilli, zygomycetes and many types of yeast. Because not all fungi are easily recognised in H&E stained sections, special stains are subsequently performed to allow identification based on characteristic morphology. Of these the Grocott-Gomori methenamine sliver (GMS) and Periodic Acid Schiff (PAS) stains are the most widely used. Another stain, calcofluor white, is a fluorescent brightener that binds to cellulose and chitin in fungal cell walls and fluoresces with a blue-white colour when exposed to UV radiation. Conventional stains are sometimes unsuccessful at identifying fungi, and therefore fungal cultures should also be routinely taken and analysed.

Invasive Fungal Sinus Disease

1) Acute fulminant sinusitis

Clinical presentation

Acute fulminant sinusitis has earned the reputation of the most acutely fatal fungal infection known to man. It is a rapidly progressive syndrome characterised by the invasion of fungi from the nasal mucosa into the sinuses, orbit and brain. A high index of suspicion in the proper clinical setting is paramount for prompt diagnosis and treatment. Typically, patients are immunocompromised by diabetes, burns, HIV, haematological malignancy or chemotherapy, but some cases have been reported in apparently healthy individuals. Fever, nasal crusting, perinasal anaesthesia, epistaxis, periorbital swelling and headache are the most common presenting symptoms. A black necrotic eschar is seen on the nasal mucosa in 80% of cases and is secondary to tissue infarction due to vascular invasion. If left untreated, progression leads to orbital cellulitis, orbital apex syndrome, cavernous sinus thrombosis and eventually fatal involvement of the central nervous system (Case 1).

Mycology/ Histology

The causative organisms are usually saprophytic fungi of the order Mucorales, including Rhizopus, Rhizomucor, Absidia and Mucor, but the condition can also be caused by Aspergillus and many other fungal species. To determine mucosal invasion, adequate specimens of sinus content containing diseased and healthy mucosa must be obtained for histopathological analysis. Because time is of the essence, fast-acting calcofluor white fungal stains should be asked for immediately on the aspirated material. Biopsy specimens of necrotic tissue should also be obtained and evaluated with frozen section if the immediate evaluation of the aspirate material is negative. Histologically, fungal hyphae can be seen to invade into surrounding tissues, causing vasculitis with thrombosis, haemorrhage and tissue infarction. When Mucor is involved, histopathology reveals characteristic large, irregularly shaped, non-septate fungal hyphae that branch at right angles. In contrast, Aspergillus can be identified due to its smaller, narrow hyphae and dichotomous branching at a 45° angle. Fungal cultures should also be taken for analysis, preferably before the initiation of any systemic antifungal treatment but may take days or weeks to grow.

Imaging

Sinus CT is indicated as soon as the possibility of invasive fungal disease is considered. Mucosal thickening of the paranasal sinuses without air-fluid level and spotty destruction of bone can be seen early in the disease process. Later, orbital spread may occur through the

Case 1 – Acute fulminant sinusitis

A 32-year old male developed left-sided facial pain and peri-orbital swelling whilst receiving treatment for severe aplastic anaemia. MRI revealed complete left-sided sinus soft tissue thickening, with almost complete blockage of the left frontal sinus and evidence of left periorbital cellulitis (Fig 2). Amphotericin B was commenced, but his symptoms continued to worsen. Nasal swabs confirmed a growth of Rhizopus arrhizus. Further MRI showed involvement of the orbit with dehiscence of the lamina papyracea and extension of disease into the anterior skull base beneath the left olfactory gyri, but no intracerebral involvement. Endoscopic debridement of the left paranasal sinuses was performed. Pathology showed areas of soft tissue infarction, necrotic bone and broad, branching non-septate hyphae consistent with Rhizopus. He continued to receive systemic anti-fungal therapy for the next 2 months and treatment for his aplastic anaemia but developed increasing confusion. CT confirmed a primary intra-ventricular haemorrhage with resulting hydrocephalus, and this resulted in his death.

Figure 2. Coronal MRI showing enhancement of intra-orbital inflammatory tissue and of mucosa over non-enhancing polypoid tissue within the maxillary sinus.
paper-thin lamina papyracea by direct extension or via the ethmoid vessels. Inflammatory involvement of the superior ophthalmic vein and ophthalmic artery have also been described on CT as radiological signs specific to orbital apex syndrome.\textsuperscript{11} MRI has a role in patients with invasive disease who have evidence of intracranial involvement or who have symptoms such as stroke, seizure or diplopia. Sinus radiograph changes are very non specific in this compromised patient group and cannot be relied upon; in one study up to 42\% of patients with leukaemia had abnormal sinus radiographs.\textsuperscript{14}

**Treatment**

Treatment of acute fulminant sinusitis should combine correction of the underlying medical condition, appropriate systemic antifungal therapy and surgical debridement. Treatment must be instituted without delay once the diagnosis is suspected. Several surgical procedures have been described in the literature depending on the extent of fungal disease at the time of diagnosis including; debridement of necrotic mucosa, Caldwell-Luc procedure, medial maxillectomy, ethmoidectomy, sphenoidectomy and radical maxillectomy with orbital exenteration. Most authors agree that standard medical therapy should be systemic amphoterocin B in a dose of 1.0 to 1.5 mg/kg/day for a period of several weeks to several months, depending on the clinical response and the degree of drug side effects, especially nephrotoxicity.\textsuperscript{15,16} Despite these treatment methods, mortality rates remain between 50 and 80\%.\textsuperscript{17,18}

**2) Chronic invasive sinusitis**

**Clinical presentation**

Chronic invasive sinusitis is by contrast a more indolent, slowly progressive invasive fungal infection that elicits limited inflammation and usually occurs in diabetic patients. Few case reports have been published and it has only recently been recognised as a specific subtype of FSD.\textsuperscript{12} Nasal symptoms are often minimal and symptoms directly related to fungal invasion may take months or years to appear. Orbital apex syndrome, characterised by decreasing visual acuity and ophthalmoplegia\textsuperscript{16} is a common presenting symptom, as are headaches, seizures and cranial nerve deficits. The disease course is variable, but death can occur due to mycotic aneurysm, internal carotid artery rupture and cavernous sinus thrombosis.\textsuperscript{20}

**Mycology/ Histology**

Aspergillus is the most commonly identified fungal organism and can be detected using fungal stains and nasal cultures.\textsuperscript{21} Other associated fungi include Alternaria, Curvularia, Bipolaris and Drechslera (Fig 3). Nasal endoscopy typically reveals friable, chronically inflamed mucosa. Histological analysis of affected tissue reveals characteristic mucosal invasion with an associated low-grade inflammatory infiltrate and associated granulomas and giant cells.\textsuperscript{21}

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**Figure 3.** Fungal species associated with FSD

**Imaging**

Sinus CT is again the recommended initial imaging modality and demonstrates sinus soft tissue thickening and altered adjacent bone. MRI is recommended in those who have signs or symptoms of intracranial disease extension and is especially helpful in evaluating the orbit, cavernous sinuses and brain.

**Treatment**

Little is known about the most appropriate treatment of chronic invasive disease as there have been so few cases published in the literature. Most published cases have been treated similar to acute fulminant sinusitis, with a combination of surgery and antifungal therapy.\textsuperscript{12,20} Choice of antifungal therapy depends on the fungal species present, although amphoterocin is the agent classically used. The duration of therapy depends on the location of residual disease and response to treatment. Prognosis tends to be poor however and recurrence is common.\textsuperscript{22}

**3) Granulomatous invasive sinusitis**

**Clinical presentation**

In 1967 a small case series of immunocompetent patients with chronic granulomatous sinusitis with associated proptosis was described in the Sudan.\textsuperscript{23,24} Similar cases have since been described in North America and Asia, but with a wider variety of fungal species.\textsuperscript{23} Proptosis is the commonest mode of presentation in these patients, but the infection may spread out of the sinuses to affect the dura and brain. On intranasal examination, there may be a firm granulomatous mass that is ulcerated or covered with overlying debris or dried secretions.\textsuperscript{23,24}
The Otorhinolaryngologist 2006; 1(1): 4-11

Fungal Sinus Disease - Core knowledge and literature review

Mycology / Histology

Aspergillus flavus is almost always the responsible organism in cases of granulomatous invasive disease. The dry climate in the Sudan, high content of Aspergillus spores in soil and high atmospheric dust content are thought to be predisposing factors. Histological examination shows extensive fungal growth with regional tissue invasion and non-caseating granulomas with giant cells, lymphocytes, histiocytes and plasma cells.26

Imaging

CT and MRI are again useful to determine extent of disease invasion. CT shows profuse soft tissue thickening with regional tissue and bony invasion. The granulomatous inflammatory response may cause pressure necrosis as well as direct invasion of bone. Proposis may be seen on MRI if the orbit is breached.

Treatment

In the 1960s Sudanese series, patients were treated by surgical debridement of granuloma, with the provision of enhanced sinus aeration and drainage via a Caldwell-Luc procedure. In many cases the condition recurred and surgery had to be repeated; the results were generally poor.26 No long term follow up of these patients has ever been published. Oral antifungal treatment may however decrease the rate of recurrence after surgery. In 1992 Gumaa et al27 published a series of 22 patients who had excision of granulomatous material and treatment with 100mg itraconazole bd for 6 weeks with good results. If clinical, radiological and serological cure was achieved, the dosage was reduced to 100mg od for 12-19 months. Partial responders continued on the same dose until resolution and non-responders were given 100mg tds until resolution. Of the 19 patients for whom follow up data was available, 62% were rated as being in complete remission in a mean 17 months after the end of therapy.

Non-Invasive Fungal Sinus Disease

1) Fungal Ball

Clinical presentation

Fungal ball disease is a non-invasive form of FSD, caused by an accumulation of compressed fungal hyphae lying on the surface of the sinus mucosa. The condition tends to affect the elderly and shows a 2:1 female preponderance. Presenting symptoms include facial pain, nasal discharge, nasal obstruction and chronic cough.28 Classically the condition involves a single sinus, most commonly the maxillary, although several sinuses can be involved.

Mycology / Histology

Virtually all fungal balls are caused by Aspergillus species, with A. fumigatus and A. flavus being the most commonly responsible organisms identified. Fungi are notoriously difficult to culture in fungal ball disease.28 Nasal endoscopy commonly reveals viscous clay-like material within the affected sinus. Histopathology of this material shows a matted, dense conglomeration of hyphae separate from but adjacent to the sinus mucosa. The mucoosa itself is characterised by a chronic, non-granulomatous inflammatory response of variable intensity to adjacent fungal elements (Fig 4). There is no fungal invasion of mucosa, associated blood vessels or bone.29

Imaging

CT reveals a rim of soft-tissue attenuation along the bony walls of the involved sinus that is completely, or almost completely, opacified. Several well-defined hyperdense foci that are variable in size can be detected. In the past these have been interpreted as misplaced dental fillings or post-traumatic foreign bodies.30 Air-fluid levels may be seen and surrounding bone can be thickened by the inflammatory process or secondary to pressure from longstanding disease.

Treatment

Endoscopic surgical resection appears to be largely curative in cases of fungal ball, without the need for systemic antifungal therapy (Case 2). Klossek’s trial of endoscopic sinus surgery (ESS) in 109 cases of fungal ball disease showed only 4 recurrences within a mean follow-up period of 29 months.31 In this study, affected maxillary sinuses were treated with a middle antrostomy or a combination of middle and inferior antrostomies. Sphenoid localisations were managed by simple sphenoidotomies and frontal involvement was treated with an infundibulotomy plus pre-operative sinus irrigation. Fungal ball cases associated with mortality tend to be sphenoid sinus lesions, in which associated intracerebral vascular complications occur as a result of sphenoid sinus surgery.28
2) **Allergic fungal sinusitis**

Allergic fungal sinusitis (AFS) is a non-invasive fungal inflammatory disorder found in patients with chronic, often intractable, rhinosinusitis and nasal polyposis. Initially recognised more than 20 years ago because of its histological similarity to allergic bronchopulmonary aspergillosis, AFS is a condition that has stimulated enormous amounts of research. Management of patients with AFS continues to present a great challenge to the ENT surgeon and controversy surrounding the aetiology, pathogenesis and appropriate treatment of the condition persists.

**Pathophysiology**

AFS is characterised by eosinophilic mucus within the sinuses, within which there is histological evidence of fungi, combined with systemic fungal specific IgE-mediated allergy. Systemic evidence of fungal allergy is demonstrated by positive serum fungal-specific IgE or positive skin-prick tests.

Although the pathophysiology of AFS remains unclear, one popular theory by Manning et al suggests that an atopic host is exposed to fungi during normal nasal respiration, providing an initial antigenic stimulus. Gell and Coombs Type I (IgE) and III (immune complex) mediated reactions then trigger an intense eosinophilic inflammatory response. The resulting inflammation leads to obstruction of the sinus ostia, resulting in stasis within the sinuses and creating an ideal environment for further proliferation of fungus. The cycle becomes self-perpetuating and results in the production of thick eosinophilic mucin, which then obstructs the involved sinuses and propagates the whole process. Clinically these patients are usually atopic, mildly asthmatic and have unilateral (50%) or bilateral polyps and plugs of sticky eosinophilic mucin within their sinuses.

Although an IgE-mediated allergic pathogenesis is presumed in AFS, a central causal link between fungal allergy and AFS is not sustained. The AFS literature tends to suffer from inconsistent definitions of AFS, retrospective clinical reports, lack of studies using comparable fungal antigens and limited comparisons with disease controls. Importantly some patients with AFS do not demonstrate allergy to the fungi identified in their eosinophilic mucus but may have elevated IgE levels to other fungi. To further compound this issue, there are many patients who do not fulfil the diagnostic criteria for AFS, but whose clinical presentation is indistinguishable from AFS.

**Eosinophilic Mucus Chronic Rhinosinusitis**

These observations led to the suggestion that AFS belonged to a wider group of conditions called eosinophilic mucus chronic rhinosinusitis (EMCRS), which has several categories defined by the variable combination of fungal presence within eosinophilic mucin and demonstration of host allergy to that fungus.

Thus patients with fungi in their eosinophilic mucus without fungal allergy are termed non-allergic fungal eosinophilic sinusitis (NAFES) or chronic fungal sinusitis (CFS). Similarly, eosinophilic mucus is considered pathognomic of the presence of fungi in the sinuses, but often fungi are not seen on microscopy or cannot be isolated. Those who do not have fungi in their eosinophilic mucus but have fungal allergy are termed AFS-like. Others simply have eosinophilic mucus and are termed nonallergic, nonfungal eosinophilic sinusitis (NANFES) or chronic eosinophilic rhinosinusitis. The common feature linking all of these patients is the presence of eosinophilic inflammation of the sinus mucosa, eosinophilic mucus and polyps. The pathophysiological and clinical relevance of this new classification system however remains to be ascertained.
Fungal Sinus Disease - Core knowledge and literature review

To add to the controversy, in 1999 Ponikau et al. demonstrated the presence of fungi in 93% of 101 patients undergoing surgery for any form of chronic rhinosinusitis by using an exquisitely sensitive fungal culture technique. Of note, the presence of fungi was also identified within 100% of the control subjects used for comparison, demonstrating that the mere presence of fungi in the nose and sinuses does not always confer pathogenicity. Further evaluation of these patients revealed fungal-specific allergy to be uncommon and the authors failed to correlate allergy to fungi with their pre-conceived definition of AFS. It was proposed that virtually all forms of chronic rhinosinusitis were related in some fashion to non-allergic eosinophilic inflammation caused by fungal exposure, rather than typical IgE-mediated inflammation, and that the term AFS should be replaced with EFRS (eosinophilic fungal rhinosinusitis). Such a study added weight to the argument the IgE-mediated inflammation perhaps plays only a contributory role in a complex overall inflammatory cascade responsible for the ultimate development of AFS and other forms of EMCRS.

## Mycology/ Histology

Fungal cultures are required to identify the responsible fungus. Frequently the cultures show no growth, or in favourable conditions, more than one fungus is identified. Bipolaris and Curvularia, both members of the dematiaceous family, are similar to Aspergillus species in being narrow, septate hyphal organisms. Histological examination of the eosinophilic mucin of patients with AFS shows an accumulation of intact and degenerating eosinophils, Charcot-Leyden crystals (eosinophilic breakdown products), cellular debris and sparse fungal hyphae. The adjacent sinus mucosa has a mixed cellular inflammatory infiltrate and there is no evidence of tissue invasion.

## Imaging

A recent study of sinus CT scans of 45 patients with AFS suggested bilateral involvement in 51% of cases, with 78% of cases showing asymmetric involvement of the paranasal sinuses. Bone erosion and extension of disease into adjacent anatomic areas was encountered in 20% of patients and was more likely to occur in the presence of bilateral advanced disease. This appearance reflects pressure-induced necrosis of bone rather than true invasion, resulting from the pressure of expanding polyps and inspissated mucin. Areas of high attenuation were found within the expanded paranasal sinuses in all patients. Typically there is heterogenicity of opacification with the less intense density of mucosal thickening and the more intense density of the mucin plugs. The authors point out that the CT specificity of diagnosing AFS could not be inferred from these findings because of the retrospective design of the study.

## Treatment

For many patients, diagnosis is an often complicated and insidious process; most do not present with all of the diagnostic criteria immediately and it may take years for an elevated serum IgE or eosinophilic mucin to develop, or for there to be positive CT results or fungal cultures. Indeed many have had multiple sinus operations by the time of diagnosis.

The effective treatment of AFS requires both medical and surgical therapy. The goal of surgery should be to remove all fungal mucin and re-establish drainage...

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### Figure 6. Eosinophilic Mucus Chronic Rhinosinusitis

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<tr>
<th>Diagnosis</th>
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<td>AFS</td>
<td>Fungal allergy + fungi detected in eosinophilic mucus</td>
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<tr>
<td>AFS-like</td>
<td>Fungal allergy but no fungi detected in eosinophilic mucin</td>
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<tr>
<td>Non-allergic fungal eosinophilic sinusitis</td>
<td>Fungal allergy absent but fungi present in eosinophilic mucin</td>
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<tr>
<td>Chronic fungal sinusitis</td>
<td>Fungal allergy absent but fungi present in eosinophilic mucin</td>
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<tr>
<td>Non-allergic, non-fungal eosinophilic sinusitis</td>
<td>No fungal allergy and no fungi in eosinophilic mucin</td>
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Bipolaris specifia, Curvularia lunata and Aspergillus fumigatus are the commonest fungi identified. Bipolaris and Curvularia, both members of the dematiaceous family, are similar to Aspergillus species in being narrow, septate hyphal organisms. Histological examination of the eosinophilic mucin of patients with AFS shows an accumulation of intact and degenerating eosinophils, Charcot-Leyden crystals (eosinophilic breakdown products), cellular debris and sparse fungal hyphae. The adjacent sinus mucosa has a mixed cellular inflammatory infiltrate and there is no evidence of tissue invasion.
pathways and physiological mucous clearance from all affected sinuses, whilst preserving normal mucosa. This can usually be accomplished endoscopically. Patients who present with nasal polyps may have their normal intranasal landmarks obliterated by the pathological lesions and may profusely bleed from their inflamed mucosa. Some advocate the use of systemic corticosteroid therapy 1-2 weeks before surgery to shrink the polyps and reduce blood loss. However, the use of prednisolone preoperatively may inhibit the identification of fungal hyphae and eosinophils in eosinophilic mucin.

Medical treatment for AFS is unlikely to be successful without adequate initial sinus surgery and it has been well established that both medical and surgical management must be co-ordinated for an optimal outcome. Recurrence of the disorder is not unusual, even with seemingly adequate surgical and postoperative medical treatment. The initial apparent connection between the disease process of AFS and allergic bronchopulmonary aspergillosis led to the introduction of oral and inhaled corticosteroid as standard medical therapy. Topical intranasal steroids have been ineffective when used alone but may have a long term preventative role after a course of oral corticosteroid or after surgery. Schubert and Goetz studied the role of systemic corticosteroids in the postoperative management of AFS, demonstrating a significant increase in the time to revision sinus surgery in those patients who received prolonged courses of postoperative oral corticosteroids. Corticosteroid therapy in this study ranged from 2 -12 months, with improved outcomes recorded among those patients who were placed on longer courses. At the present time, optimal dosing regimen and length of therapy remain unclear, and continued steroid use continues to be associated with a myriad of potential complications and side-effects.

With evidence supporting IgE-related fungal hypersensitivity in the pathogenesis of AFS, immunotherapy was proposed as a possible adjuvant therapy. Initial studies revealed apparent clinical improvement. A longitudinal study of a cohort of patients treated with immunotherapy and followed up for three years showed a significant decrease in disease recurrence and dependence on systemic and topical corticosteroids. In addition, immunotherapy after surgical removal of eosinophilic mucin resulted in a significant decrease in the rate of re-operation. Long term results have been less conclusive however. In a 10-year follow-up, immunotherapy failed to show a significant impact on long term disease control.

### References

### Acknowledgment
Dr G O’Neil, Consultant Radiologist at Glasgow Royal Infirmary, for his help with CT / MRI images.

### Figure 7. Summary of treatment options for FSD

**Acute**
- Treat underlying disease

**Fulminant**
- Systemic amphoterocin B
- ESS

**Chronic invasive**
- Little data
- ESS
- Systemic antifungal

**Chronic**
- Little data
- ESS
- Systemic antifungal

**Granulomatous**
- ESS

**Fungal ball**
- Combined medical/ surgical approach
- ESS
- Corticosteroid
- oral/ inhaled
- - Optimum dose/ route

**Allergic fungal**
- Antifungal therapy - no benefit
- Immunotherapy – no long term benefit

**Conclusion**
Currently, there is no evidence to support the use of systemic or topical antifungal therapy and studies done in this area have been inconclusive. Ponikau et al randomised, placebo-controlled trial of nasal lavage containing amphoterocin B in patients with AFS refractory to other therapies showed an improvement in CT disease appearance and on endoscopic examination, but no correlation with improvement in patient symptoms. The role of simple saline lavage and antihistamines also remains unclear at present.

**Acknowledgment**
Dr G O’Neil, Consultant Radiologist at Glasgow Royal Infirmary, for his help with CT / MRI images.
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