

Subcutaneous calcification as a supportive radiologic finding for diagnosis of rhinofacial entomophthoromycosis

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Abstract

Rhinofacial entomophthoromycosis is an uncommon chronic fungal infection of the head and neck. The diagnosis is usually based on clinical manifestations; however, diagnosis of this infection based on early manifestations is difficult and occasionally rhinofacial entomophthoromycosis is mistaken for other diseases. Therefore, computed tomography is introduced to support the diagnosis. Radiologic findings were non-specific with swelling of the sinonasal mucosa and perinasal region. However, subcutaneous calcification, that was observed in all our cases, may be a supportive radiologic evidence for diagnosis. The diagnosis should be confirmed definitively using histopathology or fungal culture. Early diagnosis allows prompt and appropriate treatment that will achieve excellent outcomes. We suggest that subcutaneous calcification radiologic finding may guide the aware physician to an early diagnosis of rhinofacial entomophthoromycosis.

Introduction

Zygomycosis can be caused by two major pathogenic orders of fungus, Mucorales and Entomophthorales. Members of the Mucorales (*i.e.* *Mucor* spp.) are angioinvasive pathogens with an aggressive clinical presentation. Pathogens within the Entomophthorales (*i.e.*

Conidiobolus spp. and *Basidiobolus* spp.) are usually more indolent. *Basidiobolus* spp. cause subcutaneous entomophthoromycosis, whereas *Conidiobolus* spp. cause rhinofacial entomophthoromycosis.¹

Rhinofacial entomophthoromycosis is extremely rare fungal infection of the head and neck region. It commonly presents as a facial subcutaneous mass or a submucosal nasal mass. Incidence is more frequent in immunocompetent patients, especially males, adults and farmers.^{1,2} The pathogenesis of rhinofacial entomophthoromycosis may be caused by inhalation, contact or traumatic implantation.^{1,2} The clinical presentations are difficult to distinguish from other conditions including Pott's puffy tumor and T-cell lymphoma. Definitive diagnosis is very important because treatment options for each of these conditions are completely different. Currently, the *gold-standard* for diagnosis of rhinofacial entomophthoromycosis is pathologic assessment or fungal culture. However, these processes may take several days to confirm a diagnosis. Therefore, we developed this study to present the clinical manifestations and computerized tomography findings of rhinofacial entomophthoromycosis for early awareness and improved management.

Case Reports

Case #1

A 61-year-old male farmer complained of progressive forehead swelling and gradually increasing nasal obstruction accompanied by sneezing, rhinorrhea and epistaxis for three months. The patient had no significant illness in the past and no history of trauma or insect bites. He underwent bilateral endoscopic widening of the maxillary ostium based on findings from computed tomography (CT) that showed mucoperiosteal thickening at the both maxillary sinuses with soft tissue density at the right osteomeatal complex causing mild right maxillary sinusitis. After surgery and administration of systemic antibiotics, his clinical picture did not improve. One month later, he was referred to our clinic at Srinagarind Hospital. We observed a diffuse swelling of the forehead and dorsum of nose (Figure 1A). Nasal endoscopy showed hypertrophy of both inferior turbinates. The middle meatus could not be clearly examined. Serologic tests were negative for Anti-neutrophilic cytoplasmic autoantibody and anti-HIV. We requested CT scan for reevaluation and this showed showed mucoperiosteal thickening of all

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sinuses. Severe swelling of prefrontal soft tissue was observed, with a small internal calcification without adjacent bony destruction (Figure 1B). Endoscopic sinus surgery was performed to widen the ostium and sinonasal tissue was taken for pathology assessment. Furthermore, subcutaneous tissue from the prefrontal area was removed for pathological examination via bicoronal forehead flap. The pathologist reported that the morphologic features and tissue reactions were consistent with rhinofacial entomophthoromycosis (Figure 2). Thus, 200 milligrams of itraconazole twice daily was prescribed for six months. The patient's symptoms were completely resolved in response to treatment and he experienced no recurrence during one year follow up (Figure 1C).

Case #2

A 56-year-old male farmer with no underlying disease or previous drug allergy, presented with progressive left unilateral

nasal obstruction for 8 months. He complained of minimal left nasal discharge and an occasional small amount of blood-stained discharge from the left nasal cavity which resolved spontaneously in each episode. At that time, he also developed progressive left nasal dorsum swelling without any fever or tenderness over the area. He complained of left epiphora but had normal visualization and no diplopia. Neither facial numbness nor neck mass was observed. He had no previous history of maxillofacial trauma, insect stings, tuberculosis contact or family history of head and neck cancer. Nasal endoscopy revealed a swelling of left inferior turbinate with a totally occluded left nasal cavity (Figure 3A and B). Other physical examinations revealed no abnormalities. CT scan showed an infiltrative soft-tissue lesion at the left inferior turbinate with extension to subcutaneous soft tissue at the left perialar and nasal dorsum region. An intra-lesional calcified spot was noted (Figure 3C). Nasal endoscopic biopsy was performed via an incision just anterior to the anterior end of the inferior turbinate. Deep biopsy in a superolateral direction above the pyriform aperture was done. The pathologist reported broad hyphae with eosinophilic sheaths, the so called Splendore-Hoeppli phenomenon, a finding compatible with a diagnosis of rhinofacial entomophthoromycosis. Itraconazole, 300 milligrams twice a day, was administered. No further surgical debridement was performed. Nasal congestion relief was observed after one month of treatment (Figure 3D). However, administration of itraconazole was planned to continue for at least 6 months. At the 3-month follow up, we found no recurrence of the disease.

Case #3

An 83-year-old female, retired farmer presented with a small right nasolabial cyst for two years. Two months previously, she had complained of a progressive painless swelling of the dorsum and tip of the nose (Figure 4A) and bilateral nasal obstruction with minimal nasal discharge. Nasal endoscopy revealed swelling of inferior turbinate with total occlusion of both nasal cavities. CT scan showed an infiltrative soft tissue lesion involving the right nasal cavity, nasal septum, both nostrils, upper lip and subcutaneous parts of the adjacent area. An intralesional calcified spot was present (Figure 4B). The nasolabial cyst was removed and the infiltrative tissue was biopsied. Hematoxylin and eosin staining of sections showed a Splendore-Hoeppli reaction and Gomori Methenamine-Silver stain showed aseptate hyphae of fungus.

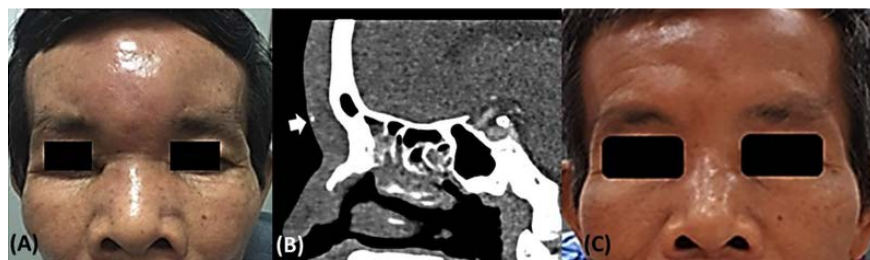


Figure 1. (A) Case #1 was a 61-year-old male farmer. Swelling of forehead and dorsum of nose was observed in the preoperative period. (B) A calcified spot (arrow) was present in the subcutaneous layer on computed tomography scan. (C) His symptoms were completely resolved in response to treatment and he experienced no recurrence during one-year follow up.

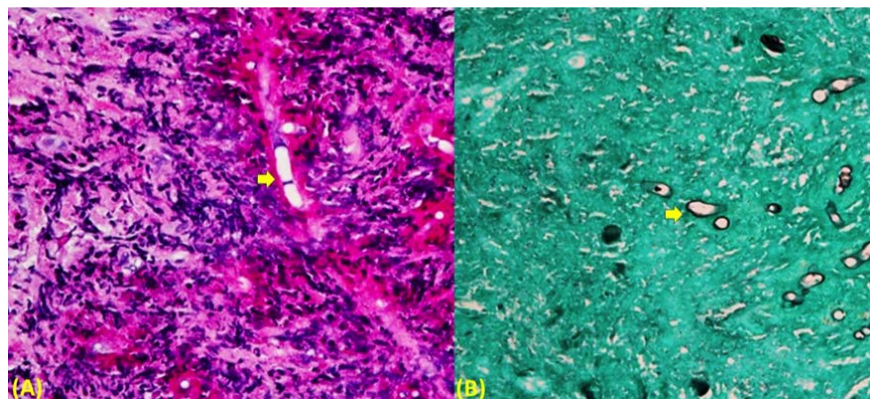


Figure 2. (A) Hematoxylin and eosin staining of sinonasal tissue from case 1 revealed non-necrotizing granulomatous inflammation with multinucleated giant cells and eosinophils. The centers of granulomas showed nonpigmented, wide-caliber, pauci-aseptate, ribbonlike hyphae with right-angle branching surrounded by Hoeppli-Splendore phenomenon material. (B) Gomori Methenamine-Silver stain also demonstrated fungal organism.



Figure 3. (A) Case #2, a 56-year-old male farmer, presented with swelling of the left dorsum of the nose. (B) Nasal endoscopy revealed swelling of the left inferior turbinate and left lateral nasal wall with totally occluded left nasal cavity. (C) A subcutaneous calcified spot was seen on computed tomography scan (arrow). (D) One month after treatment, decreased swelling of left lateral nasal wall was observed.



Figure 4. (A) Case #3 was an 83-year-old female retired farmer. She complained of swelling of the dorsum and tip of the nose. (B) Computed tomography scan revealed an infiltrative lesion at nasal tip and perialar with intralesional calcified spot (arrow). (C) She had responded well to treatment after one month.

Itraconazole, 300 milligrams twice daily was prescribed for 6 months. She had responded well to treatment after 1 month (Figure 4C). She remains under follow up. Asymptomatic with no disease recurrence was observed for 3 months.

Discussion

Rhinofacial entomophthoromycosis is caused by saprophytic fungi of the genus *Conidiobolus* that are normally found in soil and decaying plant materials. The causative organisms are most common in tropical and subtropical areas.³ All of our patients were rice farmers from the north-east of Thailand, a region with a humid and tropical climate. Although rhinofacial entomophthoromycosis has low incidence, it has high morbidity and mortality. The common clinical presentations are progressive unilateral nasal obstruction due to inferior turbinate swelling and non-tender subcutaneous infiltrative mass at the dorsum of nose, upper lip and eyelid.^{1,2} However, deeply invasive and atypical forms have been reported in which patients present with progressive submucosal pharyngeal involvement and developed dysphagia and laryngeal obstruction.⁴ Therefore, early diagnosis is very important. Diagnosis of rhinofacial entomophthoromycosis is usually based on clinical manifestations. However, early manifestations of this infection can easily be mistaken for other diseases including T-cell lymphoma, Pott's puffy tumor, and tuberculosis.

Recently, CT scanning has been introduced to assist in assessment of disease. In rhinofacial entomophthoromycosis, several previous studies^{1,2,4} reported that an infiltrative soft-tissue lesion at the inferior turbinate or lateral nasal wall could extend to the overlying subcutaneous tissue at perialar or adjacent region such as the cheek, upper lip or eyelid. These non-specific characteristics may be found in other diseases. Usually, the CT appearance of fungal calcification is a hallmark to support diagnosis of fungal ball sinusitis. The calcification develops from metabolic deposits of calcium within the mycelial mass. Kopp *et al.*⁵ and Stammberger *et al.*^{6,7} reported that a focal hyperdense area with calcium phosphate and calcium deposits within the necrotic area of the mycelium could be observed on plain radiographs. This subcutaneous calcification was also observed in all our cases and might be helpful in diagnosis of rhinofacial entomophthoromycosis. However, a similar finding may occur in other diseases

including insect sting, subcutaneous injection, systemic lupus erythematosus, dermatomyositis, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, basal cell nevus syndrome, subcutaneous lipodystrophy, venous thrombosis, pilomatrixoma,⁸ and calcinosis cutis following acne vulgaris.⁹ Therefore, presence of a subcutaneous calcification on CT should be correlated with clinical manifestations. Confirmed diagnosis of rhinofacial entomophthoromycosis is usually established by histopathology and/or fungal culture. A typical pathognomonic finding of this condition is broad hyphae with an eosinophilic sheath, the so-called Splendore-Hoeppli phenomenon.¹⁰ However, histopathology may be inconclusive if a sampled specimen or biopsy is from a site where visible fungus is not present. Transverse-cut hyphae may appear as empty halos with eosinophilic cuffing. Inexperienced examiners may not recognize them as hyphae. A further diagnostic difficulty is that culture attempts are often unsuccessful. Yang *et al.*¹¹ suggested use of Malt extract glucose yeast extract peptone agar medium to culture this fungus.

There have been too few reports of rhinofacial entomophthoromycosis to permit development of a standard treatment protocol. Various antifungal regimens have been proposed. Okafor and Gugnani¹² recommended saturated potassium iodide solution (SSKI) (1-3 g/day) and cotrimoxazole as the drugs of choice in developing countries due to low cost and absence of serious adverse effects. In cases resistant to SSKI, monotherapy or combination treatment with other drugs, such as fluconazole, itraconazole and terbinafine has been reported to be efficacious and relatively safe. In our series, 400-600 milligrams/day of itraconazole were administered. All patients showed complete resolution of disease with no recurrence during the follow-up period.

Surgical resection is reserved for cases with extensive infection and resistance to medical treatment. Aggressive surgical removal may induce rapid spread of infection and produce extensive fibrosis, which further leads to poor response to medical treatment and recurrence.^{13,14} Gupta *et al.*¹⁵ reported five patients who underwent nasal/sinus or facial surgery before the diagnosis. Three of them had poor response/relapsed after stopping medical treatment. In contrast, our first case, who underwent endoscopic sinus surgery and resection of prefrontal subcutaneous tissue, responded well to medical treatment and was in remission after completing the course of medication. This outcome may

affect from varied extended resection. However, surgical resection is not necessary for removal of infected tissue because the disease responds well to medical treatment. Thus, surgery should be reserved for resection of residual disease.

Conclusions

Finding of subcutaneous calcification in CT scans may guide the aware physician to an early diagnosis of rhinofacial entomophthoromycosis, thus permitting prompt antifungal treatment which is likely to achieve excellent outcomes and avoid complications.

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