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Primary cutaneous facial phaeohyphomycosis due to *Verruconus gallopava* (*Ochroconus gallopava*) in an immunocompetent woman from the Sub-Himalayas – a case report and literature review

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Abstract
Verruconus gallopava is a melanised environmental saprophyte. Human infections of respiratory and central nervous systems occur primarily in immunocompromised subjects. Skin and subcutaneous infections are seen when disease involves multiple sites. Primary cutaneous phaeohyphomycosis is exceptional. We report a case of an immunocompetent female who had facial phaeohyphomycosis with V. gallopava following trauma. Lesions progressed despite antibiotic therapy. Diagnosis was established on fungal culture and she showed some favourable response to itraconazole 200 mg with terbnafine 250 mg at her second visit but was lost to follow up. No single therapeutic regimen is consistently efficacious in V. gallopava infections. Early laboratory confirmation is imperative to achieve success as outcome is variable even with combination of antifungal agents and surgery.
Keywords: *Verruconus gallopava, phaeohyphomycosis, itraconazole.*

Introduction

Verruconus gallopava, a dematiaceous fungus is an environmental saprophyte and rarely pathogenic. Organ transplant, haematological malignancies and advanced HIV infection constitute the risk factors [1-3]. Pulmonary or cerebral infections occur frequently and cutaneous and subcutaneous disease is seldom encountered [3-6]. Diagnosis may be missed due to lack of clinical suspicion. Response to systemic antifungal therapy with itraconazole (ITR), voriconazole (VOR) and amphotericin B (AMB) is unpredictable in advanced disease. We report primary cutaneous facial phaeohyphomycosis due

to *V. gallopava* showing initial response to oral ITR.

Case Report

A 50 years old Nepalese woman injured her right cheek with a wooden splinter following which a non-healing painful, red lesion appeared. She visited a peripheral health institution where empirical amoxicillin with clavulanic acid 625 mg T.I.D with topical antibiotics were prescribed. Dermatological consultation was taken as there was negligible response after two weeks of therapy. We saw the lady with a well to ill defined erythematous, crusted, indurated, tender plaque of 2.5X3.5 cm size over a diffuse swelling of right cheek [Fig.1].

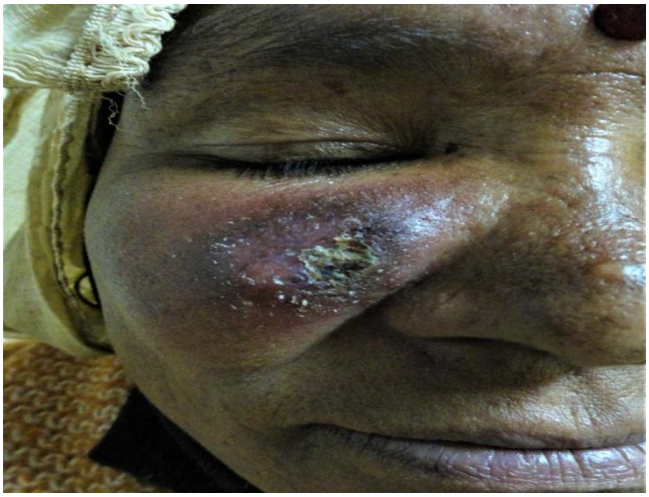

Figure 1 Erythematous, crusted, indurated, plaque of 2.5X3.5 cm size over a diffuse swelling of right cheek

Rest of skin, hair and nails were healthy. General physical examination was non-contributory, vitals were within normal range and there were no systemic features. Laboratory investigations revealed absence of diabetes, HIV infection, tuberculosis or malignancies.

Considering phaeohyphomycosis provisionally, skin biopsy was subjected to histopathology which revealed a granulomatous lesion. Direct microscopy of sample revealed sparse septate hyphae.

Fungal culture on SDA with chloramphenicol grew olivaceous mould at 25°C which had a characteristic surrounding reddish brown diffusible pigment [Fig. 2].

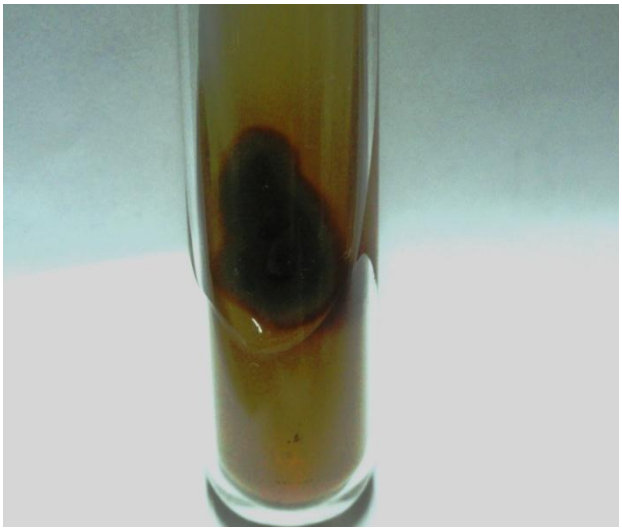

Figure 2 Dark olivaceous velvety growth with surrounding reddish pigment characteristic of *Verruconus gallopava* seen on Sabouraud's dextrose agar

Micro-slide culture showed pigmented, septate hyphae with conidigenous cells bearing characteristic brown ovoid to clavate conidia on cylindrical denticles, grouped in two and constricted at the central septum consistent with *V. gallopava* [Fig. 3].

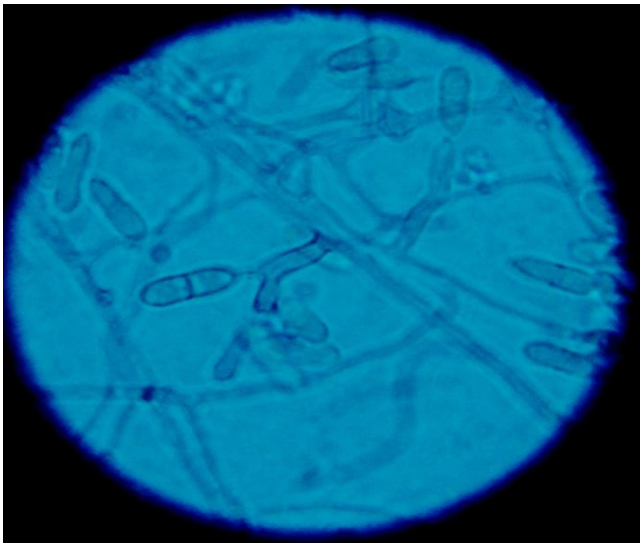

Figure 3 Pigmented, septate hyphae with conidigenous cells bearing clavate conidia of *Verruconus gallopava* on cylindrical denticles constricted at the central septum (cotton blue staining, 100X).

A repeat biopsy was cultured and patient was instituted itraconazole 100mg B.D. The lesion showed minimal regression after one month therefore terbinafine 250 mg daily was added. On the next review, there was good response.

Meanwhile the fungal culture of the second biopsy also showed growth of *V. gallopava*. The identity of the isolate was confirmed at the National Culture Collection of Pathogenic Fungi (NCCPF), PGIMER, Chandigarh, as *V. gallopava* (accession number 380006). The final outcome could not be documented as patient was lost to follow up.

Table: Cases of *Verruconus gallopava* infection reported in literature

No.	Year/Ref	Sex	Age	Site involved	Predisposition	Therapy	Outcome
1	Dixon et al, 1986, USA [25]	ND	ND	Lung	ND		ND
2	Fukushiro et al, 1986, Japan [2]	F	58	Subcutaneous abscess	AML	5-FC	Survived
3	Terrani et al, 1990, USA [15]	M	62	Lungs, liver , kidney, brain	CLL	None	Died
4	Sides et al, 1991, ND [13]	M	ND	Lung	I/C	ND	ND
5	Sides et al, 1991, South Africa [13]	ND	ND	Lung	Coal mine worker	ND	ND
6	Sides et al, 1991, South Africa [13]	ND	ND	Lung	Coal mine worker	ND	ND
7	Sides et al, 1991, USA [13]	ND	ND	Lung	I/C	ND	ND
8	Sides et al, 1991, USA [13]	ND	ND	Brain	I/C	ND	ND
9	Sides et al, 1991, USA [13]	M	47	Lung	Cardiovascular disease	ND	ND
10	Sides et al, 1991, USA [13]	M	60	Brain	Lymphoma, nocardiosis	Craniotomy, AMB, 5-FC, fluconazole	died
11	Mancini et al, 1992, USA [26]	M	30	Pulmonary nodule	SOT (heart)	AMB	survived
12	Smith et al, 1993, ND [27]	M	46	Cerebral abscess	SOT(heart)	None	died
13	Vukmir et al, 1994, USA [28]	M	68	Cerebral abscess	SOT (liver)	AMB, 5FC, ITR	survived
14	Kralovic et al, 1995, USA [29]	M	63	Lung, brain, disseminated	SOT (liver)	AMB, ITR, surgery	died
15	Rossmann et al, 1996, USA [30]	M	59	brain	SOT (liver)	AMB	died
16	Bonham et al, 1996, USA [31]	ND	ND	brain	SOT (liver)	ND	survived
17	Jenney et al, 1998, Australia [32]	M	58	Pulmonary nodule	SOT (heart), diabetes	AMB, ITR	survived
18	Horre et al, 1999, UK [12]	ND	ND	Systemic	AIDS	ND	ND
19	Horre et al, 1999, Australia [12]	ND	ND	Systemic	ND	ND	ND
20	Horre et al, 1999, USA [12]	ND	ND	brain	Diabetes mellitus	ND	ND
21	Horre et al, 1999, ND [12]	M	48	lung	SOT, HIV positive	ND	ND
22	Horre et al, 1999, Australia [12]	ND	ND	lung	ND	ND	ND
23	Horre et al, 1999, USA [12]	ND	ND	lung	SOT	ND	ND
24	Burns et al, 2000, Canada [21]	F	58	Lung, skin	SOT (lung)	AMB, ITR	survived
25	Odell et al, 2000, USA [7]	M	38	Multiple lung abscess	Wood pulp worker	Surgery (lobectomy), ITR	survived
26	Bowyer et al, 2000, UK [17]	M	69	Eye(endophthalmitis)	CLL	AMB intravitreal, ITC, fluconazole	died
27	Mazur et al, 2001, USA [33]	F	32	lung, shoulder abscess, brain abscess	SOT(lung), diabetes	AMB, 5FC, ITR, surgery	survived
28	Malani et al, 2001, USA [5]	M	32	Lung, brain, thyroid	SOT (kidney), diabetes	AMB, ITR, FCZ	died
29	Zhao et al, 2002, China [18]	M	68	Lung	pemphigus	AMB, ITR	survived
30	Wang et al, 2003, China [4]	M	13	Disseminated, brain, lung, spleen	SOT (kidney)	AMB, ITR, VOR	died
31	Bravo et al, 2004, USA [23]	M	72	lung	Alcohol abuse, MAC infection lung	ITR	survived
32	Fukushima et al, 2005, Japan [16]	F	66	Brain, lung, femoral mass	CLL	AMB, 5-FC,ITR,terbina-fine	died
33	Ohori et al, 2006, USA [19]	M	54	systemic	SOT (heart)	ND	died

34	Ohori et al, 2006, Japan [19]	M	79	lung	pneumoconiosis	ND	ND
35	Ohori et al, 2006, Canada [19]	F	68	lung	ND	ND	ND
36	Ohori et al, 2006, USA [19]	ND	ND	lung	ND	ND	ND
37	Ohori et al, 2006, New Zealand [19]	M	83	lung	ND	ND	ND
38	Boggild et al, 2006,Canada [3]	M	28	Lung, brain, hip joint	Advanced HIV	VOR, caspofungin	died
39	Hollingsworth et al,2007, USA [24]	F	79	lung	I/C (previous basal cell carcinoma and surgically cured melanoma)	VOR	survived
40	Shoham et al, 2007, USA [10]	F	64	lung	SOT(kidney)	AMB, VOR, fluconazole	survived
41	Shoham et al, 2007, USA [10]	M	60	lung	SOT (kidney)	ITR	survived
42	Shoham et al, 2007 [10]	M	50	lung	SOT (liver)	VOR	survived
43	Mayer et al, 2009, USA [34]	ND	ND	lung	SOT (kidney)	ND	ND
44	Wong et al, 2010, New Zealand [6]	M	58	peritoneum	SOT(heart)	VOR	survived
45	Qureshi et al, 2012, USA [1]	M	53	Lung, spine	SOT(kidney)	AMB, VOR	died
46	Qureshi et al, 2012, USA [1]	M	54	lungs	SOT(B/L lungs)	AMB, VOR	survived
47	Qureshi et al, 2012, USA [1]	M	66	lung	SOT(lung)	VOR	survived
48	Qureshi et al, 2012, USA [1]	F	57	lung	SOT (lung)	VOR	survived
49	Qureshi et al, 2012, USA [1]	F	60	lung	SOT(heart)	ITR	survived
50	Qureshi et al, 2012, USA [1]	M	57	lung	SOT(B/L lungs)	Lobectomy , ITR	died
51	Qureshi et al, 2012, USA [1]	F	58	lung	SOT (lung)	AMB, ITR	survived
52	Qureshi et al, 2012, USA [1]	M	67	brain	SOT (liver)	AMB, ITR	died
53	Qureshi et al, 2012, USA [1]	M	69	brain	SOT (liver)	AMB, ITR	survived
54	Qureshi et al, 2012, USA [1]	M	53	Lung, spine; abscesses	SOT (kidney)	Surgical drainage, AMB,VOR	survived
55	Qureshi et al, 2012, USA [1]	M	55	ND	SOT (lung)	ITR	survived
56	Meriden et al, 2012, USA [14]	M	34	Lung	Chronic granulomatous disease, on therapy - AMB, 5-FC, Interferon for Aspergillosis	ITR, VOR pneumonectomy,posaconazole	survived
57	Desangles et al, 2013, France [20]	M	55	Lung, subcutaneous, brain, peritoneum	SOT(heart), diabetes	VOR	died
58	Kumaran et al, 2013, India [22]	M	55	Skin, hyperkeratotic plaques	I/C, Gardner	ITR, terbinafine	died
59	Karthika et al, 2014, India [35]	F	30	Allergic fungal rhinosinusitis	I/C, agricultural worker	Surgery, steroids and topical antibiotics	survived
60	Present case	F	50	Facial skin	Manual labourer	ITR, terbinafine	died

Footnote ; F female; M male; AML acute myeloid leukaemia; CLL chronic lymphatic leukaemia; I/C Immunocompetent; B/L bilateral; 5-FC 5 flucytocine; SOT solid organ transplant; AIDS acquired immunodeficiency syndrome; ITR itraconazole; VOR voriconazole; AMB amphotericin B; ND not determined.

Discussion

Phaeohyphomycosis encompasses infections due to melanised fungi and *Verruconus gallopava* is rarely encountered. The nomenclature of *Verruconus gallopava* has evolved from *Diplorhinotrichum gallopavum*, *Dactylaria gallopava* to the genus *Scolecobasidium* [7]. In 1983, de Hoog classified it under *Ochroconus* and recently it is christened as *Verruconus gallopava* [7-9]. It is an environmental fungus occurring in soil, decaying vegetation and hot springs[7,10]. It has caused epidemic encephalitis in birds [11]. Only 59 human infections are scripted in world literature primarily from the USA, Australia, China, Canada, Japan, New Zealand and India [Table 1]. In the review of the demographic profile of 46 cases, male to female ratio was 3.2:1. Majority, 73.3% (33/45) acquired infection in their fifties and no case was reported in children below ten years [Table 1]. Poverty of immunity

was predisposing factor in 80% cases. Solid organ transplant was reported as risk factor in 52.5% cases and other conditions included diabetes, HIV/ AIDS, [3,11,12], lymphoma [13,14] and haematological malignancy [2,15-17]. Cardiovascular accident, pemphigus, pneumoconiosis, chronic granulomatous disease and steroid therapy were antecedent in few [12-14,18,19].

V. gallopava is a pneumotrophic and neurotropic fungus. The inhaled fungal spores establish granulomatous reaction in the respiratory tract. Early asymptomatic infection followed by cavitary or non-cavitary lesions and abscesses develop in lungs and if suspected and detected then is amenable to treatment associated with a good clinical response. Literature reveals 50% cases having only pulmonary involvement [Table 1]. More often respiratory infection remains unabated and *Verruconus* sp. spreads to the central nervous system due to its neurotropism causing cerebral infection or abscess. Joint, kidney, thyroid, spine and liver are affected in cases when multiple system involvement [1,3,5,15].

Secondary cutaneous and subcutaneous lesions have been described in subjects having *Verruconus sp.* infection of lung or brain with leukaemia, solid organ transplant and diabetes [2,20,21]. Primary cutaneous phaeohyphomycosis is rare, recognised in one Immunocompetent case. The present case is second in this regard having localized primary cutaneous lesion following trauma and repeat isolation of *Verruconus gallopava* confirmed at NCCPF, PGIMER, Chandigarh established diagnosis[22].

Systemic fungal invasion by *V. gallopava* accounts for high mortality of 46-80% [3,23]. Early recognition and timely therapeutic intervention may save a precious life but either the infection is not provisionally considered or pathogenic role may not be ascribe due to lack of awareness. Thus, diagnosis is demanding and management is challenging. Of the 40 cases reporting a final outcome, 24 (60%) have survived and 16 (40%) succumbed to infection despite therapy with multiple antifungal agents and surgery [10,11, 22].

A variety of treatment regimens have been tried based on clinical experiences but optimal therapy remains ambiguous. The antifungal prescriptions employed frequently include ITR, AMB and VOR. ITR is consistently potent and flucytosine reasonably effective especially when toxicity of AMB is a concern [1,7,10,23]. VOR is a useful alternative with potent antifungal activity and broad spectrum against black fungi. It has an advantage of maintenance of therapeutic serum levels and effective concentration in the CSF and tissue [14, 24]. AMB is advocated in life-threatening phaeohyphomycosis when benefits are weighed against toxicity[8]. Echinocandins and posaconazole have shown excellent in-vitro activity and provide future therapeutic substitutes for *V. gallopava* infections but no case of remedial assessment is documented so far[8].

Experience of treating cutaneous phaeohyphomycosis due to *Verruconus* is inconstant. Patients with secondary cutaneous or subcutaneous affliction along with involvement of other body sites treated with 5-FC, AMB and ITR recovered [2,21] whereas a patient given VOR succumbed to infection [20]. The only reported case of primary skin condition was managed on oral terbinafine 250 mg daily, ITR 200 mg twice daily for four months followed by parenteral AMB. The outcome was not encouraging as initial healing process was interrupted probably due to secondary systemic spread of fungal infection and septicemic shock [22]. It is difficult to comment on final outcome of the present case as was lost to follow up. Year wise distribution of *Verruconus gallopava* cases reported in literature showing age, sex, site involvement, predisposing factors, therapy and outcome shown in table 1. *Verruconus gallopava* must be considered provisionally in subjects with primary cutaneous phaeohyphomycosis as early diagnosis and effective treatment prevent systemic spread and fatal outcome.

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