

Subcutaneous Phaeohyphomycosis Caused by *Pyrenochaeta romeroi* in a Rheumatoid Arthritis Patient: A Case Report with Review of the Literature

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Abstract *Pyrenochaeta romeroi* is a rare fungal agent of chronic, suppurative subcutaneous infections leading to mycetoma. It is an unusual cause of deep, non-mycetomatous infections. We herein present review of the literature along with a case of 61-year-old Indian female with rheumatoid arthritis who developed subcutaneous phaeohyphomycosis caused by *Pyrenochaeta romeroi*. It posed a diagnostic challenge, as the culture from fine-needle aspirate revealed a non-sporulating dematiaceous mould, which was the only supportive tool for its diagnosis and initiation of the therapy. However, it was the molecular sequencing which played the pivotal role in clinching the final aetiological diagnosis. To the best of our knowledge, this is the 20th case of *Pyrenochaeta* species infection occurring worldwide and first case report of subcutaneous phaeohyphomycosis caused by *Pyrenochaeta romeroi* in a rheumatoid arthritis patient.

Keywords Phaeohyphomycosis · Subcutaneous · Rheumatoid arthritis · *Pyrenochaeta romeroi*

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Introduction

Members of genus *Pyrenochaeta* are phaeohyphomycotic and saprophytic fungi which are distributed widely in environmental niches; i.e. in soil, wood, thorns and plant debris. The classification of the species in the genus *Pyrenochaeta* and allied genera is still under revision and is debatable. To date, only four species, namely *Pyrenochaeta romeroi* (*P. romeroi*), *P. mackinnonii*, *P. unguis-hominis* and *P. keratinophila*, have been found to cause human infections. Recently, *P. romeroi* has been renamed as *Medicopsis romeroi* [1, 2]. *P. romeroi* is the most interesting and upsurging fungus causing opportunistic infections. It was first described by Borelli in 1959 [3]. The most common route of infection is through traumatic inoculation. It is mainly prevalent in tropical, subtropical regions and less frequently in temperate countries [4]. It has been occasionally implicated in the aetiology of chronic cutaneous and subcutaneous infections [1]. Paucity of the knowledge about the factors involved in causing subcutaneous phaeohyphomycosis by *P. romeroi* and lack of standard treatment prompted us to report this rare case of a 61-year-old Indian rheumatoid arthritis woman. A comprehensive review of the literature of the rare *Pyrenochaeta* species is also discussed.

Case Report

A 61-year-old female, resident of Kanpur, Uttar Pradesh (India), housewife by profession, presented

to the outpatient department of the hospital, with gradually increasing painless swelling over right index finger since last 2 months. She also gave a history of early morning stiffness with multiple joint pains involving hands and feet since last 10 years. There were no other constitutional or systemic symptoms, but her medical records revealed that she was a known case of rheumatoid arthritis on treatment with a disease-modifying antirheumatic drug (DMARD)—methotrexate (15mg/week) but had been taking oral corticosteroids—prednisone (10mg) whenever there were exacerbations of joint pains since last 10 years. There was no history of any trauma at the site of infection, other major ailments like diabetes, hypertension, tuberculosis, epilepsy or any surgical interventions. Her travel history was non-contributory. On physical examination, moderate anaemia was observed. Local examination revealed a soft-to-firm, non-tender, immobile, non-discharging, well-defined, 2×2 cm swelling at the proximal phalanx of the right index finger. The overlying skin was unremarkable, and it was free from underlying structures (Fig. 1). Movement of the right index finger was little restricted, but there was no neurological deficit. On systemic examination, no abnormality was detected.

Her abnormal laboratory parameters were : microcytic hypochromic anaemia with haemoglobin level of 9 g/dl



Fig. 1 Subcutaneous swelling at proximal phalanx of the right index finger

(MCV-70.6 fl); the peripheral blood total leucocyte count of 12,000/ml with differential being of 70 % neutrophils, 18 % lymphocytes, 8 % monocytes, 4 % eosinophils, a platelet count of 5,10,000/ μ l; the erythrocyte sedimentation rate of 60 cu mm/h; and C-reactive protein 80 g/dl. Liver and renal function tests were normal. Fasting and postprandial blood sugar were within normal limits. Rheumatoid arthritis factor was elevated (18 IU/ml). Serological tests for HIV, hepatitis B and C antigen were non-reactive. X-ray bilateral hands and wrist showed diffuse osteopenia of bones with reduction in joint spaces. Multiple soft tissue densities were noted over bilateral wrist joints with another soft tissue density over right second digit proximal phalanx (Fig. 2).

Fine-needle aspiration cytology (FNAC) of the right index finger swelling was performed, which yielded 2 ml of dirty yellow purulent pus mixed with blood without any discrete granules. After the aspiration, the swelling reduced completely. Microscopic examination of May–Grunwald–Giemsa stained smears revealed few septate fungal hyphae in the background of degenerated acute as well as chronic inflammatory cells and necrosis. Periodic acid-Schiff (PAS) stained smears showed presence of PAS-positive branched septate hyphal elements with irregular swellings (Fig. 3). A portion of specimen was sent for microbiological tests. Direct examination by KOH (10 %) mount showed dematiaceous septate hyphae. On calcofluor white stain, fluorescent septate fungal hyphae were seen. The specimen was cultured by standard techniques onto the routine media for isolation of the agent. The pyogenic and mycobacterial cultures were sterile, while those for fungi were positive for a dematiaceous mould. Culture was inoculated on a duplicate set of Sabouraud's dextrose agar with and without antibiotics and was incubated at 25 and 37 °C, respectively. After 20th day of incubation, grey-black velvety colonies were seen (Fig. 4). Lactophenol cotton blue mount of the colonies revealed brown septate hyphae. The microslide culture on potato dextrose agar was done, which revealed a non-sporulating dematiaceous mould. A subculture was done on oat meal agar which revealed a grey black mould after 5 weeks. Lactophenol cotton blue mount showed brown septate mycelium with brown-black pycnidia.

The isolate was provisionally identified as *Pyrenochaeta* spp., on the basis of gross and microscopic features; hence, it was further sent for sequencing of the internal transcribed spacer (ITS) regions of



Fig. 2 X-ray showing soft tissue density at *right* second digit proximal phalanx along with the features of rheumatoid arthritis

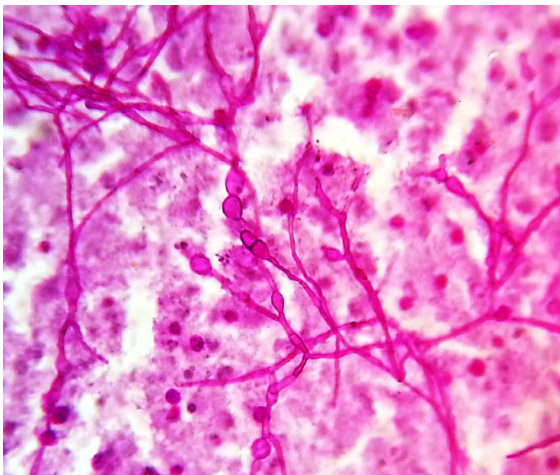


Fig. 3 Periodic acid-Schiff's (PAS) stain revealing PAS-positive septate fungal hyphae with irregular swellings (X400)

ribosomal DNA (rDNA) at National Culture Collection for Pathogenic Fungi (NCCPF), Post Graduate Institute of Medical Research and Education



Fig. 4 Grey-black velvety colonies on Sabouraud's dextrose agar

(PGIMER), Chandigarh. Meanwhile, the swelling was incised and drained out completely. The patient was started on antifungal therapy with itraconazole (200 mg/day for 3 months) and was advised not to use oral corticosteroids while the dose of methotrexate was reduced (7.5mg/week). Subsequently, the isolate at NCCPF was identified as *P. romeroi* by ITS1, ITS2, ITS4 and D1, D2 sequencing. After 6 months of follow-up, the patient was asymptomatic and no recurrence was observed (Fig. 5).

Discussion

Most phaeohyphomycotic infections are caused by *Exophiala*, *Phialophora* and *Cladophialophora* species. *Pyrenochaeta* spp. are rare cause of subcutaneous phaeohyphomycosis (phaeohyphomycotic cyst/phaeosporotrichosis) which is a localized infection of the deep dermis and subcutaneous tissues caused by dematiaceous fungi [5]. Table 1 shows the clinico-mycological profile of patients with *Pyrenochaeta* spp. worldwide. After careful review of pertinent literature till date [1–4], [6–21], of the 19 cases reported so far of *Pyrenochaeta* spp., nine were

reported as subcutaneous phaeohyphomycosis, seven presented as black grain mycetoma, two as keratitis and one case of onychomycosis. The most common species isolated was *P. romeroi* (15 cases), followed by one each of *P. unguis-hominis*, *P. mackinnonii* and *P. keratinophila*. A new species of *Pyrenochaeta* causing keratitis has also been isolated, which is still unnamed. Recently, there has been a rise in the incidence of *P. romeroi* causing subcutaneous phaeohyphomycosis. Most of these cases have been reported in immunocompromised patients. Immunocompromised conditions documented in the literature causing *P. romeroi* infection were post-renal transplantation (3), use of steroids for leprosy (1), asthma (1), acute lymphoblastic leukaemia (1) and diabetes (1). Two cases were seen in healthy individuals. History of trauma in the past was absent in most of the cases. Epidemiologically, most of the patients with this infection were Indian in origin. In India, the isolations were mostly from North Indians. Most of the cases reported worldwide were cured, though one case was resistant to the therapy, while one patient expired due to co-morbid condition. In these cases of subcutaneous phaeohyphomycosis, surgical drainage or excision with antifungal treatment was done in five cases. Itraconazole was the drug of choice in six cases, voriconazole in one case; additional use of posaconazole and amphotericin B was done in one case each, while in two cases, surgical drainage or excision without any antifungal treatment was done. However, topical cefazolin, amphotericin B, ofloxacin, natamycin drops with oral ketoconazole and fluconazole were the treatment given to a keratitis case [13]. The onychomycosis patient died before the start of the therapy due to other associated ailments [10].

There has been a recent increase in the incidence of phaeohyphomycosis [21], which is perhaps being attributed to the growing number of immunocompromised patients, as was seen in this case. This female patient aged 61 year old, resident of Kanpur, Uttar Pradesh (North India), was a known case of rheumatoid arthritis who was on intermittent long-term steroid therapy since last 10 years. There could be two precipitating factors for this infection i.e. unrecognized traumatic inoculation or longterm immunosuppression from corticosteroids leading to immunocompromised state and delayed clinical expression. Though, she did not recall any inciting trauma, possibility of an innocuous trauma occurring during her domestic activities could not be ruled out, as she was a housewife who used to handle and cut vegetables in routine. To the best of our



Fig. 5 Right index finger showing a resolved lesion on post-treatment follow-up

Table 1 Review of all *Pyrenochaeta* species cases reported worldwide

S.no.	References	Species	Country	Age (years)/sex of the patient	Risk factor	Clinical presentation	Diagnosis	Treatment	Outcome
1.	Andre et al. [6]	<i>P. romeroi</i>	Cambodia	–	Nil	Black grain mycetoma	KOH mount, culture, histopathology	–	–
2.	Baylet et al. [7]	<i>P. romeroi</i>	Senegal	–	Nil	Black grain mycetoma	KOH mount, culture, histopathology	–	–
3.	David-Chausse et al. [8]	<i>P. romeroi</i>	–	–	Nil	Black grain mycetoma, pedis	KOH mount, culture, histopathology	–	–
4.	Borelli [3]	<i>P. romeroi</i>	–	–	Nil	Black grain mycetoma	KOH mount, culture, histopathology	–	–
5.	Thammayya et al. [9]	<i>P. romeroi</i>	India	–	Nil	Black grain mycetoma, pedis	KOH mount, culture, histopathology	–	–
6.	English [10]	<i>P. unguis-hominis</i>	United Kingdom	85/F	Arthritis and domestic activities	Brownish discolouration of finger nail	Culture	Brulidine cream	Died (due to associated ailments)
7.	Serrano et al. [11]	<i>P. mackinnonii</i>	Venezuela	39/M	Accidental injury	Painless pseudotumor of the back of the right toe	Histopathology	Excision, itraconazole	Cured
8.	Mohanty et al. [12]	<i>P. romeroi</i>	India	36/M	Nil	Inflammatory mass over right foot with multiple discharging sinuses	KOH mount, gram stain, culture	–	–
9.	Girard et al. [4]	<i>P. romeroi</i>	France	45/M	Immunosuppression due to steroid intake for multibacillary leprosy	Large subcutaneous flaccid lesion at lateral side of the left leg	Histopathology, culture	Incision and drainage, itraconazole	Cured

Table 1 continued

S.no.	References	Species	Country	Age (years)/sex of the patient	Risk factor	Clinical presentation	Diagnosis	Treatment	Outcome
10.	Ferrer et al. [13]	<i>Pyrenochaeta</i> (new species)	Europe	77/F	Diabetes	Unresponsive bacterial keratitis with pain and decreased vision in the left eye	Gram stain, calcofluor white stain, culture, sequencing	Topical ceftazolin, amphotericin B, ofloxacain, natamycin, oral ketoconazole and fluconazole	Lesion improved, but cornea damaged
11.	Cerar et al. [14]	<i>P. romeroi</i>	United Kingdom (Pakistani in origin)	56/M	Nil	Localized swelling at lateral side of right foot	Histopathology, culture, sequencing	Itraconazole, flucytosine—9 months, Posaconazole—17 months	Resistant to the treatment
12.	Badali et al. [1]	<i>P. romeroi</i>	India	45/F	Nil	Verrucous plaque and a swelling at right forearm	KOH mount, histopathology, culture, sequencing	Excision of the cyst, no antifungal therapy	Cured
13.	Verkley et al. [15]	<i>P. keratinophila</i>	Europe	–	Nil	Keratitis	KOH mount, culture, sequencing	–	–
14.	Khan et al. [16]	<i>P. romeroi</i>	Kuwait (Indian origin patient)	47/F	Immunosuppression due to maintenance therapy for ALL	Swelling over the proximal interphalangeal joint of the right index finger	KOH mount, histopathology, culture, sequencing	Repeated drainage, no antifungal therapy	Cured
15.	Thiyagarajan et al. [17]	<i>P. romeroi</i>	United Kingdom (South Asian origin patient)	57/M	Immunosuppressive therapy with prednisolone for renal transplantation	Nodular lesion on the left knee	Histopathology, sequencing	Excision, voriconazole	Cured
16.	Ocampo et al. [18]	<i>P. romeroi</i>	France (Central African Origin patient)	66/M	Immunosuppressive therapy with prednisolone for renal transplantation	Verrucous, skin-coloured, hyperkeratotic painless nodule (wart-like) on the left heel	Histopathology, culture, sequencing	Reduction in immunosuppressive therapy, excision	Cured

Table 1 continued

S.no.	References	Species	Country	Age (years)/sex of the patient	Risk factor	Clinical presentation	Diagnosis	Treatment	Outcome
17.	Hsiao et al. [19]	<i>P. romeroi</i>	Taiwan	78/M	Immunosuppression due to steroid intake for asthma	Papulopustular lesions on an erythematous to purpuric plaque over the right upper limb	Sequencing	Itraconazole-6 months, Amphotericin B-3 weeks	Cured
18.	Chan et al. [20]	<i>P. romeroi</i>	Singapore	55/M	Immunosuppressive therapy with prednisolone for renal transplantation	Nodular lesion at left posterior thigh	Histopathology, culture, sequencing	Multiple excisions, Itraconazole	Responded to the treatment (Died due to acute MI)
19.	Yadav et al. [21]	<i>P. romeroi</i>	India	50/F	Diabetes	Swelling over left foot	FNAC, KOH mount, culture, sequencing	Incision and drainage, Itraconazole	Cured
20.	The present case	<i>P. romeroi</i>	India	61/F	Immunosuppression due to steroid intake for rheumatoid arthritis	Swelling over proximal phalanx of right index finger	FNAC, KOH mount, culture, sequencing	Reduction in immunosuppressive therapy, Incision and drainage, Itraconazole	Cured

P Pyrenochaeta, *M* male, *F* female, *ALL* acute lymphoblastic leukaemia, *MI* myocardial infarction, *FNAC* fine-needle aspiration cytology

knowledge, it is the tenth case of *P. romeroi* subcutaneous infection and first case to be reported in a rheumatoid arthritis patient.

Clinical lesions of phaeohyphomycosis are non-specific, sometimes deceptive and usually present as subcutaneous, indolent nodules at the site of the initial trauma [22]. The outcome is often protracted with evolution towards a cold abscess and/or local necrosis and may form fistula in the skin with a chronic purulent discharge in cases of immune deficiency.

The diagnosis was elicited by direct microscopy and culture of fine-needle aspirate. Characteristic pycnidia formation on oat meal agar after 5 weeks clinched the aetiological agent as *Pyrenochaeta* spp. The isolate could only be identified and confirmed by sequencing of the ITS regions of rDNA. Out of the nineteen cases reported in the world literature, in ten cases molecular sequencing played an integral role in identifying and confirming its diagnosis. The identification of *Pyrenochaeta* spp. is difficult because some strains do not produce characteristic diagnostic structures in culture as well as limited expertise is available in most of the diagnostic microbiology laboratories [16]. Still, mycological examination with direct examination and culture on specific media remains absolutely mandatory for an accurate identification of the fungus [4].

Data on the antifungal susceptibility of the *Pyrenochaeta* spp. remain scarce due to the low availability and number of clinical isolates, difficulty in growing the fungus in culture and little knowledge about the relation between the minimal inhibitory concentration (MIC) and clinical outcome of *Pyrenochaeta* infection [1, 14]. We could not attempt antifungal susceptibility, as there are no guidelines available in Clinical and Laboratory Standards Institute (CLSI) protocol for fungi producing pycnidia. Though some authors have reported that isavuconazole, posaconazole, terbinafine and ketoconazole have potent in vitro activity against *P. romeroi* [1, 17], others have reported it to be resistant to amphotericin B, fluconazole and caspofungin [1, 14], with variable effect to voriconazole [14, 16, 17]. Itraconazole was shown to be potent by Badali et al. [1], but resistant by Cerar et al. [14].

The optimal management approach and standard effective treatment for infections associated with melanized fungi have not been well established [23, 24]. Therefore, surgical excision of the entire

lesion is usually curative in maximum number of cases. Though, the literature shows that the patients with *Pyrenochaeta* spp. infections show good response to both surgical drainage and debridement of the infected lesion along with prolonged use of one of the triazoles (itraconazole) [1, 25]. Some authors have also mentioned the reduction in the lesion with drainage alone without the use of antifungal drugs. The present case responded very well to the incision and drainage along with itraconazole therapy, which is consistent with the results in other reports of subcutaneous phaeohyphomycosis caused by *P. romeroi* [4, 21].

This case underscores the need to suspect, diagnose and strictly follow up the cases of skin and soft tissue fungal infections, especially in immunocompromised patients, so as to prevent its dissemination. Furthermore, *P. romeroi* is a rare fungi, whose identification by cultures is difficult as well as data pertaining to its antifungal susceptibility is scarce. However, an early attempt for its aetiological diagnosis should be made, especially in immunocompromised patients via various techniques like FNAC or biopsy, which not only aid in detection, but also play an important therapeutic role for such infections. This case also highlights the importance of identifying a phaeohyphomycotic non-sporulating, pycnidia-producing mould by sequencing, as this affects the overall patient management.

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