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Advances in microbiology, infectious diseases and public health: Refractory *Trichophyton rubrum* infections in Turin, Italy: a problem still present

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Copyright Year	2015
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Author	Family Name Tullio Particle Given Name Vivian Suffix Division Bacteriology and Mycology Laboratory, Department of Public Health and Pediatrics Organization University of Torino Address via Santena 9, 10126 Turin, Italy
Author	Family Name Cervetti Particle Given Name Ornella Suffix Division Department of Medical Sciences Organization University of Turin Address Turin, Italy
Author	Family Name Roana Particle Given Name Janira Suffix Division Bacteriology and Mycology Laboratory, Department of Public Health and Pediatrics Organization University of Torino Address via Santena 9, 10126 Turin, Italy
Author	Family Name Panzone Particle Given Name Michele Suffix Division A.O.U. Città della Salute e della Scienza Organization San Lazzaro Hospital Address Turin, Italy
Author	Family Name Scalas

Particle
Given Name **Daniela**
Suffix
Division Bacteriology and Mycology Laboratory, Department of
Public Health and Pediatrics
Organization University of Torino
Address via Santena 9, 10126 Turin, Italy

Author Family Name **Merlino**
Particle
Given Name **Chiara**
Suffix
Division Bacteriology and Mycology Laboratory, Department of
Public Health and Pediatrics
Organization University of Torino
Address via Santena 9, 10126 Turin, Italy

Author Family Name **Allizond**
Particle
Given Name **Valeria**
Suffix
Division Bacteriology and Mycology Laboratory, Department of
Public Health and Pediatrics
Organization University of Torino
Address via Santena 9, 10126 Turin, Italy

Author Family Name **Banche**
Particle
Given Name **Giuliana**
Suffix
Division Bacteriology and Mycology Laboratory, Department of
Public Health and Pediatrics
Organization University of Torino
Address via Santena 9, 10126 Turin, Italy

Author Family Name **Mandras**
Particle
Given Name **Narcisa**
Suffix
Division Bacteriology and Mycology Laboratory, Department of
Public Health and Pediatrics
Organization University of Torino
Address via Santena 9, 10126 Turin, Italy

Corresponding Author	Family Name	Cuffini
	Particle	
	Given Name	Anna Maria
	Suffix	
	Division	Bacteriology and Mycology Laboratory, Department of Public Health and Pediatrics
	Organization	University of Torino
	Address	via Santena 9, 10126 Turin, Italy
	Email	annamaria.cuffini@unito.it

Abstract Dermatophytosis caused by *Trichophyton rubrum* is the most common cutaneous fungal infection in industrialized countries and worldwide with high recurrence and lack of treatment response. In addition, patients with cutaneous and concurrent toenail lesions are often misdiagnosed and therefore treated with an inappropriate therapy. In this study, we evaluated five previously misdiagnosed cases of *T.rubrum* chronic dermatophytosis sustained by two variants at sites distant from the primary lesion. Our patients were successfully treated by systemic and topical therapy, and 1 year after the end of therapy follow-up did not show any recurrence of infection.

Our data indicate that the localization of all lesions, the isolation and the identification of the causative fungus are essential to establish the diagnosis and the setting of a correct therapeutic treatment to avoid recurrences.

Keywords (separated by '-') *Trichophyton rubrum* - Chronic dermatophytosis - Misdiagnosis

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Advances in Microbiology, Infectious Diseases and Public Health ~~Short Data Report/Revised Version~~

Refractory *Trichophyton rubrum* Infections in Turin, Italy: A Problem Still Present

Vivian Tullio, Ornella Cervetti, Janira Roana, Michele Panzone, Daniela Scalas, Chiara Merlino, Valeria Allizond, Giuliana Banche, Narcisa Mandras, and Anna Maria Cuffini

Abstract

Dermatophytosis caused by *Trichophyton rubrum* is the most common cutaneous fungal infection in industrialized countries and worldwide with high recurrence and lack of treatment response. In addition, patients with cutaneous and concurrent toenail lesions are often misdiagnosed and therefore treated with an inappropriate therapy. In this study, we evaluated five previously misdiagnosed cases of *T. rubrum* chronic dermatophytosis sustained by two variants at sites distant from the primary lesion. Our patients were successfully treated by systemic and topical therapy, and 1 year after the end of therapy follow-up did not show any recurrence of infection.

Our data indicate that the localization of all lesions, the isolation and the identification of the causative fungus are essential to establish the diagnosis and the setting of a correct therapeutic treatment to avoid recurrences.

Keywords

Trichophyton rubrum • Chronic dermatophytosis • Misdiagnosis

V. Tullio, J. Roana, D. Scalas, C. Merlino, V. Allizond, G. Banche, N. Mandras, and A.M. Cuffini (✉)
Bacteriology and Mycology Laboratory, Department of Public Health and Pediatrics, University of Torino, via Santena 9, 10126 Turin, Italy
e-mail: annamaria.cuffini@unito.it

O. Cervetti
Department of Medical Sciences, University of Turin, Turin, Italy

M. Panzone
A.O.U. Città della Salute e della Scienza, San Lazzaro Hospital, Turin, Italy

30 Chronic dermatophytosis is a condition in which
31 the clinical symptoms persist for more than 1 year
32 with episodes of exacerbation and remission (Hay
33 1982; Zaias and Rebell 2003; Prasad et al. 2005).
34 The main etiologic agent is *Trichophyton rubrum*
35 responsible for 90 % of chronic infections (Di
36 Chiacchio et al. 2014; Nenoff et al. 2014).
37 Chronicity is probably related both to fungal cell
38 wall components, such as mannan, that play an
39 important role in the process of down-modulation
40 of cell-mediated immune response of the host and
41 to a lack of treatment response (Blake et al. 1991;
42 Sato and Tagami 2003; Waldman et al. 2010).
43 Patients with cutaneous and concurrent toenail
44 lesions are often misdiagnosed and, therefore,
45 treated with an inappropriate therapy (Larruskain
46 et al. 2005).

47 In this study, we evaluated previously
48 misdiagnosed cases of *T. rubrum* chronic
49 dermatophytosis in five patients admitted to the
50 Medical Sciences Department, University of
51 Torino (Italy), through an investigation of clinical
52 and mycological infection aspects.

53 **Case 1** A 42-year old male, born in Ecuador,
54 reported a 7-year history of itchy and squamous
55 lesions on the soles, toenails, palms and the nail
56 plates, before arriving in Italy (Fig. 1a–d). Despite
57 therapies with topical antibacterial agents in his
58 native country, the patient had extensive erythema
59 with painful papules, pustules and crusts in the
60 chin and beard (Fig. 1e, f). Incomplete alopecia,
61 associated with follicular nodules most prevalent
62 above the upper lip was seen. Hands and
63 fingernails examination revealed hyperkeratosis
64 and distal onycholysis.

65 **Case 2** A Caucasian male of 48 years presented
66 erythematous and squamous lesions on the feet
67 and toenails. A closer examination revealed scal-
68 ing lesions on the inguinal area and buttocks,
69 hands and fingernails plate hyperkeratosis and
70 distal onycholysis.

71 **Case 3** A Caucasian female of 78 years reported
72 a 2-week history of extensive erythema with
73 papules and fine pustules appearing at the

opening of hair follicles in the inguinal region 74
(Fig. 2a, b). An intense erythema involved both 75
buttocks and thighs (Fig. 2c). Examination of the 76
left foot revealed sole and toenail/fingernail 77
hyperkeratosis, with nail plate thickened, friable 78
and yellowish (Fig. 2e, f). The left knee (Fig. 2d) 79
and the right leg were also involved with flaking 80
in net margins. 81

Case 4 A Caucasian female of 69 years, with 82
rheumatoid arthritis, treated for 20 years with 83
therapeutic cycles of methotrexate (7.5 mg/ 84
week) and prednisone (5 mg/day), presented a 85
chronic erythematous scaly dermatitis extended 86
to the lower back and rear thigh area, diagnosed 87
as psoriasis (Fig. 3e). Since 2006, she was treated 88
with emollient cream and topical steroids with- 89
out benefit. On physical examination, the patient 90
revealed *tinea pedis* and *tinea unguium* with sole 91
and toenails plate hyperkeratosis (Fig. 3a, b), 92
squamous lesions on the elbow, on the back and 93
left palm (Fig. 3c, d, g). Involvement of the scalp 94
with flaking dandruff and thinning hair was 95
observed (Fig. 3f). 96

Case 5 A Caucasian female of 68 years, with 97
rheumatoid arthritis, treated for several years 98
with prednisone (25 mg/day), presented a history 99
of chronic erythematous scaly dermatitis 100
diagnosed as psoriasis and treated with emollient 101
cream without benefit. A closer examination 102
revealed an intense lamellar desquamation of 103
the toenails and fingernails, hyperkeratosis of 104
the soles and the palms, scaling lesions with 105
sharp margins in the breast, abdomen, inguinal 106
area, buttocks and thighs, neck and chin. 107

Mycological analysis of all patient lesions 108
was performed. Skin and nail samples were col- 109
lected, examined under a light microscope (20 % 110
KOH + 40 % DMSO preparation) and 111
inoculated into Mycobiotic agar (Merck, 112
KGAA, Germany) to detect dermatophytes. 113
Molds identification was based on macroscopic 114
and microscopic characters of the colonies after 115
15 days of incubation at 25 °C. 116

All patients had dermatophytosis and concur- 117
rent lesions caused by two variants of *T. rubrum*: 118



Fig. 1 Case 1. A 42-year old, male, born in Ecuador. Squamous lesions on the soles, toenails, palms and nail plates (a–d); extensive erythema in the chin and beard with follicular nodules above the upper lip (e, f)

119 downy white-colored colonies with reverse pig- 126
 120 ment brownish-yellow (Cases 1, 2, and 3) or deep 127
 121 wine-red (Cases 4, and 5). Scant teardrop-shaped 128
 122 microconidia along septate hyphae were 129
 123 observed on microscopic colonies examination. 130
 124 The primary lesion was localized always in 131
 125 the foot (*tinea pedis*), in agreement with other 132

studies (Larruskain et al. 2005). Secondary 126
 lesions distributed in other sites were the main 127
 demand for medical consultation; in all five 128
 cases, the anatomical sites mainly interested 129
 were the inguinal area, buttocks, palms and 130
 fingernails (*tinea unguium*). In only one case, 131
tinea capitis was observed (Case 4). Patient 132



Fig. 2 Case 3. A 78-year old, female, Caucasian. Extensive erythema with papules at the opening of hair follicles in the inguinal region (a, b), buttocks and thighs (c); left

knee with flaking in net margins (d); toenail and fingernail hyperkeratosis (e, f)

133 4 under methotrexate therapy and patient
 134 5, under corticosteroid therapy had risk factors
 135 predisposing them to fungal spread. *Tinea* in
 136 such cases tends to be chronic and extended,
 137 mimicking various skin diseases, such as psoria-
 138 sis, eczema, etc., as in Patients 4 and 5 (Atzori
 139 et al. 2012; Tan et al. 2014).

For all patients a successful treatment with 140
 topical (azoles) and systemic (terbinafine hydro- 141
 chloride 250 mg/day) antimycotics was carried 142
 out. In details, in patient 1, after 4 weeks of 143
 treatment, all skin lesions were completely 144
 healed and culture results were negative; both 145
 direct mycological and culture were negative 146



Fig. 3 Case 4. A 69-year old, female, Caucasian, with rheumatoid arthritis. Sole and toenails hyperkeratosis (a, b); back and left palm squamous lesions (c, d); extensive

erythema on lower back and rear thigh area diagnosed as psoriasis (e); scalp with flaking dandruff and thinning hair (f); squamous lesions on the elbow (g)

147 also for nails after 3 months. In patient 2, all
148 lesions were completely healed and culture
149 results were negative after 12-weeks of treat-
150 ment. In patient 3, all skin lesions were
151 completely healed after 6 weeks of treatment;
152 both direct mycological and culture were nega-
153 tive for nails after 4 months. In patient 4, after
154 4-weeks of treatment, all skin lesions were
155 completely healed; both direct mycological and
156 culture were negative also for nails and scalp
157 after 5 months. In patient 5, after 6-weeks of
158 treatment, all skin lesions were completely
159 healed and culture results were negative; the
160 nail lesions were alleviated after 5-months
161 therapy.

162 The five clinical cases reported in this study
163 are considered dermatophytosis, affecting both
164 immunocompetent and immunodeficient
165 patients, and fulfilled the diagnostic criteria of
166 *T. rubrum* chronic dermatophytosis, as indicated
167 by the literature (Zaias and Rebell 1996;
168 Böhmer and Korting 1999; Kick and Korting
169 2001; Balci and Cetin 2008; Piñeiro
170 et al. 2010; Kong et al. 2015). Since in our
171 group of patients from the beginning a correct
172 therapeutic treatment was not carried out or
173 misapplied, a gradual spread of the infection
174 occurred to the toenails, as secondary site
175 involved, constituting the reservoir of infection
176 that spread later to other sites, such as legs,
177 groin, hands, face and scalp. On the other
178 hand, it has to be underlined that *tinea unguium*
179 is an infection usually more resistant to treat-
180 ment, whose eradication is difficult even with
181 appropriate therapy (Gupta and Cooper 2008).

182 For fungal infection eradication, diagnosis
183 must be based on both a correct patient history
184 and an adequate microbiological study that
185 includes the identification of the species isolated.
186 Therefore, it is essential a careful examination of
187 the patient *in toto* to avoid inappropriate or
188 wrong therapeutic treatment. In fact, as in the
189 first patient, the antibiotic treatment was
190 established solely on the observation of highly
191 inflammatory facial injuries that did not present
192 the typical clinical features of *T. rubrum* infection
193 (Yin et al. 2011); hence, the treatment being
194 wrong was ineffective.

In conclusion, our data indicate that in all
cases of suspected syndrome or when skin
involvement is extended to multiple sites, the
localization of all lesions, the isolation and the
identification of the causative fungus are essen-
tial to establish the diagnosis, prognosis and the
setting of a correct antifungal therapy to avoid
recurrences.

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