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Trichophyton mentagrophytes genotype VII, an emerging infection: a Systematic Review

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Parole chiave: Trichophyton mentagrophytes genotype VII; infezione emergente; trasmissione sessuale

Abstract

Background. *In the past few years there has been a dramatic change in the prevalence of the genotype VII of the Trichophyton mentagrophytes. Trichophyton mentagrophytes is a dermatophyte fungus commonly found in wild, terrestrial and burrowing animals such as rabbits, that has now adapted to an anthropophilic environment and is responsible of an emerging zoonosis.*
Study design. *A thorough background research and a systematic review have been done to show the effect of this emerging dermatophytic infection on humans.*
Methods. *Three electronic databases were searched for eligible studies: PubMed, Scopus and Web of Science. All the articles found were then screened, first, by title and abstract and, then, by full text. A quality assessment was done using the Newcastle–Ottawa Quality Assessment Scale (NOS).*
Results. *28 articles were found. 4 of which were included in this review. These articles were produced in France, Switzerland, the USA and Germany. They showed interesting clinical evidence regarding how this inter-human multidrug resistant mycosis could easily become an epidemic sexually transmitted infection.*
Conclusions *This systematic review emphasizes how the spread of this pathogen, genotype VII, in humans must not be underestimated. Consequently, in order to facilitate early intervention and, thus, avoid a multi resistant epidemic growth of this infection, new diagnostic measures are required.*

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Introduction

Recently, there has been a sudden spike in sexually transmitted infections, including the infection caused by the *Trichophyton mentagrophytes* (T.M.) genotype VII (1,2). It must not be forgotten that superficial fungal infections of the skin, otherwise known as dermatophytosis, are the most common of all mycoses. In fact, skin mycoses actually afflict approximately 20-25% of the world population (3). The frequency of these dermatomycosis has been increasing in these last few years. A combination of geographical location, a variety of environmental and cultural conditions, and the predominant anatomical infection patterns influence the distribution of dermatomycoses and the associated aetiological agents. (3,4). The dermatophyte's growth depends mainly on surface temperatures, which ideally should be between 25°C and 28°C. Moreover, a warm, moist environment can also promote skin infection.

Dermatomycoses are more common in poor social and economic conditions. The risk of contracting these fungi increases in cramped living conditions, which facilitate frequent skin-to-skin contact, close proximity to animals, as well as potentially inadequate hygienic practices. Moreover, superficial skin infections have little tendency to self-limit and inadequate/non-existent healthcare may contribute to a pandemic spread of cutaneous mycoses. Although there are local characteristics and individual predispositions to dermatophyte infections, the variety of these infections is not stable. Mass tourism, international sports events, and increased migration promote the introduction and spread of rare or previously neglected dermatophyte species (3). *Trichophyton mentagrophytes* (T.M.), a dermatophyte species, usually found in wild, terrestrial and burrowing animals such as wild rabbits, has now adapted in an anthropophilic setting. T.m. is now one of the top three most frequent fungi that cause "ringworm" in domestic animals such as rabbits and guinea pigs, but can also be found in cats and dogs (5-8).

T.M. has evolved in an anthropophilic setting. It is now one of the major causes of zoonotic skin diseases and the second most isolated fungus causing inflammatory tinea infections in humans. Based on ITS regions of rDNA gene similarity, the *Trichophyton mentagrophytes* complex includes three entities: *T. mentagrophytes* (including ITS genotypes III, III, IV, VII and IX), *T. interdigitale* (including ITS genotype II), *T. indotineae* (ITS genotype VIII) (9-11). Currently, a few genetic variations of these keratinophilic fungi have the potential to spread from one human to another (12,13). Furthermore, as reported in several studies, we are witnessing the establishment of a drug resistance against T.M., which represents a serious threat to global public health. It increases morbidity and mortality, and is associated with high economic costs due to its health care burden (4,5).

In 2002, tinea cruris (an infection involving the genital, pubic, perineal, and perianal skin), was reported in sex workers, thus, raising the possibility of dermatophytes being sexually transmitted (14). In 2009, *Trichophyton mentagrophytes* was found in a heterosexual couple who had contracted tinea gladiatorum after the index patient had contact with a presumptively infected dog (15). Moreover, Jabet et al. (demonstrated that sexual partners of infected patients have been found to have comparable lesions on multiple occasions.

In contrast to other *T. mentagrophytes* genotypes, T.M. VII has not been linked to dermatophytosis in children who interact with animals, underlining the possibility of it being a sexually transmitted infection (16). Furthermore, as reported in several studies, we are witnessing the establishment of a drug resistance against

T.M., which represents a serious threat to global public health. It increases morbidity and mortality, and is associated with high economic costs due to its health care burden (17-19).

Materials and Methods

1. Selection Protocol and Search Strategy

The current systematic review was conducted according to Preferred Reporting Methodology for Systematic Reviews and Meta-Analyses (PRISMA) (20). The protocol has been registered in PROSPERO with the following ID: CRD42024571209.

Research involved the use of three separate databases: PubMed, Scopus and Web of Science. All articles from the beginning to 19 July 2024 were then selected using the search string "*Trichophyton mentagrophytes* genotype VII".

1.1. Inclusion Criteria for the Study

All the articles found were then screened, first, by title and abstract and, then, by full text. The selection was done independently by all authors (L.C., M.S., L.P, F.G., F.P., A.Q., I.P.). The same authors individually reviewed all the papers. Any questions, doubts or inconsistencies that were found,

were resolved, between all the authors, by discussion until unanimous agreement. All research that provided any given data with regard to this microorganism or its impact/effect on humans was considered valid. Articles that contained unique information, including case reports, were considered to compensate for the limited information available. Reviews, meta-analyses, symposia and editorials, were excluded from this research. The authors only included articles that were in English or Italian.

1.2. Data Extraction and Quality Assessment

Information regarding author, year, country, sex, age, sexual orientation, co-infection, partner infection, transmission mode, lesions and therapy used was, then, extracted from all the included studies. Data were organised in order, based on the mode of transmission, the effect/impact of this emerging infection, diagnosis and treatment.

A quality assessment was done using the Newcastle–Ottawa Quality Assessment Scale (NOS). The NOS for observational studies evaluates study quality according to a set of questions, where each study can be assigned up to nine points based on three areas. The first domain, "SELECT" (4 points), considered study group selection, sample size, respondent profile, and whether the different risk factors were clearly identified. The second domain, "COMPARATIVITY" (2 points), included the comparability of different outcome groups and whether confounding factors were controlled. The final domain, "RESULTS" (3 points), examined whether verification of exposure and outcome was clearly assessed, or whether statistical testing, if used, was appropriate. The scores were then added up and the quality was considered "Good" if the total was greater than 7, "Fair" when the score awarded was between 5 and 7, or "Poor" if the final result was less than 5 (21).

Results

After a thorough research, a total of 28 studies were extracted from the following databases: PubMed, Web of Science and Scopus. Of these, 15 duplicates were removed and 13 were then screened based on title and abstract.

In the following stage, 4 articles were excluded as they did not meet the inclusion criteria previously decided by all authors. The remaining 9 articles were then reviewed by full-text.

After having reviewed all the remaining texts, 5 articles were excluded for the following reasons: 1 did not contain information concerning humans, 2 were not experimental studies, and for 1 no clinical information could be found. Finally, only those 4 articles that met the inclusion criteria were included (Figure 1).

Quality was then measured using the NOS stated above, Table 1 summarises the data extracted from the included studies.

The articles included were published in the years 2019 (22), 2020 (23), 2023 (16) and 2024 (24). These studies were conducted in France (16), Switzerland (23), the USA (24) and Germany (22). The 4 included studies described patients between the age of 22 and 59 (16, 22-24) and two reported a homosexual orientation (16,24). Most patients, in these studies, have described that they presented with the infection after having returned from a trip abroad and after sexual intercourse (16,22-24). Two of these studies reported transmission to partners (16,22).

Only one article reports the average time of 28 days between the appearance of lesions and hospital consultation (16). Lesions reported are skin lesions with scaly, erythematous eruption in the inguinal region, genitalia, legs, arms, and back (16,22-24).

Patients were submitted to to antifungal treatments (terbinafine, itraconazole, or voriconazole) systemically and/or topically (16,22-24). The follow-up was conducted every 2-4 weeks after the onset of therapy (22). The persistence of post-inflammatory pigmentation and scarring or loss of beard hair was noted (16).

The patients' sites of infection (external genitalia, buttocks, face), the high-risk STI profile, and consistent identification of T.M. VII suggest that it is a sexually transmitted infection. The lack of contact between the patients and animals also suggests the possibility of human-to-human transmission (16,22-24).

Regarding the quality assessment, only 1 study was considered "Fair", while the other 3 were considered "Good".

Discussion

Dermatophytosis caused by the fungus T.M. genotype VII, often results in the development of tinea genitalis/pubogenitalis (if the genitals and inguinal folds are affected), corporis (various parts of the body, including trunk), faciei (face), and barbae (beard). Sometimes, ulcers or abscesses can develop. The observed prevalence of the sites of infection suggest

Table 1 - Summary of the characteristics of the studies included in the review

Authors, Country, Years	n°; sex; age (range); sexual orientation	Co-infection	Travel	Partner infection	Mode of Trasmission	Lesions	Therapy	Follow-up	Conclusion	Quality assessment
Jabet A, et al. France 2023 (16)	13 M; 39 (22-59); 11 homosexual; 1 bisexual; 1 heterosexual	7 HIV positive, and 5 were taking HIV preexposure prophylaxis. 8 patients had Chlamydia trachomatis; 1 Syphilis; 3 monkeypox virus; 1 Klebsiella aerogenes	4 no outside France; 1 in Germany; 1 in Slovenia; 1 Spain; 1 India. 3 reported having had contact with animals (cats or dogs).	4 patients	Sexual intercourse	Five patients had a single skin lesion, and others had multiple lesions. One patient had inguinal papules and nodules suggestive of Majocchi granulomas, 2 had highly inflammatory folliculitis of the beard (kerion), and the others had typical erythemato-squamous lesions with an active border	9 patients received systemic antifungal treatment (terbinafine, itraconazole, or voriconazole) for 3 weeks to 4 months; 4 received only topical treatment.	3 postinflammatory pigmentation; 2 scars or beard hair loss.	Sexual trasmission is supported by the sites of the infection (external genitalia, buttocks, face), the high-risk STI profile of the patients, and consistent identification of TMVII. Lack of animal contact for most patients also suggests human-to-human transmission	good
Klinger M, et al. Switzerland 2020 (23)	for type VII 7; 2 F; 31 (26-42) No sexual orientation		3 in Thailand		Anthropophilic, sexually transmitted	Extensive ulcerations in the genital area, inguinal and anal areas, facial area	Terbinafine 3 patients for systemic therapy; 4 with a combination of systemic and topical therapy		The transmission of genotype TMVII, on the other hand, seems to be mostly due to sexual contact and appears to occur often in Thailand.. The infection frequently leads to inflammatory tinea, and therefore, patients are usually treated with oral antifungals for 8 weeks.	good

Kupsch C, et al. Germany 2019 (22)	for type VII 37; 2 F; 31 (26-42) No sexual orientation	Escherichia coli; Staphylococcus aureus	Japan, China, Russia, Georgia and Australia, Southeast Asia	5 patients	From human to human	The infections were highly inflammatory with erythematous plaques and pustules and extremely painful	Combined synergistic therapy consisting of systemic treatment with 250 mg terbinafine daily and local application of miconazole and/or ciclopirox olamine several times daily is recommended. If terbinafine therapy was ineffective, a switch to itraconazole was successful.	The success of antifungal treatment was monitored with fungal culture by sampling and mycological analysis every 2–4 weeks after the onset of therapy.	Infections occur in body parts where the fungi come into direct contact with naked skin, as can also be observed with other dermatophyte infections The hypothesis of a direct human-to-human infection via sexual contact is supported by the fact that the sexual partners of our patients were also infected in five cases..	good
Caplan AS, et al. New York 2024 (24)	1; M; 30; homosexual		Europe (England and Greece) and California		Sexual intercourse	Scaly, erythematous eruption in the inguinal region, genitalia, legs, arms, and back	Fluconazole weekly for 4 weeks with no response. 6 weeks of terbinafine with improvement. Due to persistent infection, he was transitioned to itraconazole with further improvement.		Current evidence suggests responsiveness to terbinafine, yet some patients may require itraconazole.6 Prolonged treatment duration may be necessary. When TMVII is suspected or diagnosed, sexual partners should be evaluated and the patient screened for other sexually transmitted infections.	fair

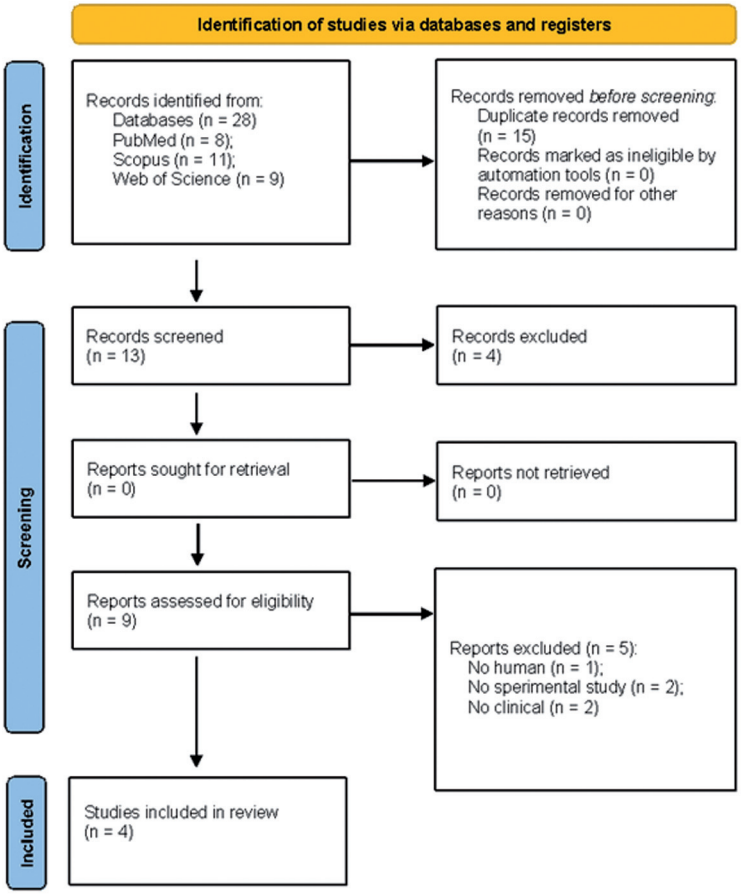

Figure 1 - PRISMA flowchart for search strategy.

that it can be sexually- transmitted, with an increase in anogenital infections (16,22-25).

Recent literature shows an alarming increase in prevalence of this infection in Europe. Transmission has been documented to have occurred in patients who have travelled to Europe or outside Europe in the previous month.

Early documented cases are those individuals who had engaged in sexual intercourse with sex-workers in Asia (16,22-24). Currently, it has been observed that infections not only occur upon return from travel, but also in gyms, and in men-who-have-sex-with-men (16,24). Even if most of the cases are documented in homosexual males, infections have also occurred in heterosexual couples and in women (16). The most affected age group has an average age of 30, usually considered the most sexually active. Another consideration is the prevalence of international travel among this age cohort (Table 1).

Notwithstanding the fact that T.M. has been described as an animal-borne infection, there have been documented cases reporting inter-human transmission. At the initial stages of infection, inflammatory lesions are usually present and are, initially, treated with antibiotics or antifungals which prove to be ineffective over an extended period of time. Routine culture searches are unable to identify the infectious agent, so sequencing of the ITS region is required to identify different species and genotypes. This increases delay in diagnosis and, also, costs (23,26). Most patients were responsive to terbinafine, but some required itraconazole due to the emergence of terbinafine-resistant strains of *T. mentagrophytes* genotype VII, administered either systemically or locally (16,22,26). Patients need a follow-up of about 4-6 weeks with periodic monitoring after eradicating the microorganism. (16,22,25).

Conclusions

This emerging infection caused by T.M. genotype VII must not be underestimated. It is very important to consider this rare, new, sexually transmitted disease (STD) when treating patients that present with inflammatory and purulent dermatophytosis at ano-genital, pubic, facial, and beard sites, and have recently returned from a trip. It is imperative to list *T. mentagrophytes* as an STD, and it is necessary to implement a screening service that can properly diagnose and detect this dermatophyte to facilitate a prompt, expedient, efficacious and appropriate treatment and thus avoid a multiresistant epidemic growth (18,19,26). As a preventive measure, an awareness campaign should be organized, highlighting the importance of protected sex especially among the most susceptible age cohort.

Riassunto

***Trichophyton mentagrophytes* genotype VII, un'infezione emergente: una revisione sistematica**

Premessa. Negli ultimi anni si è assistito a un drastico cambiamento nella prevalenza del genotipo VII del *Trichophyton mentagrophytes*. Il *Trichophyton mentagrophytes* è un fungo dermatofita, che di solito si riscontra in animali selvatici e terrestri, come i conigli, che ora si è adattato in un ambiente antropofilo ed è una zoonosi emergente.

Disegno dello studio. È stata condotta una revisione sistematica per mostrare gli effetti di questa infezione dermatofitica emergente nell'uomo.

Metodi. Sono state utilizzate tre banche dati elettroniche per la ricerca degli studi idonei: PubMed, Scopus e Web of Science. Tutti gli articoli trovati sono stati poi esaminati prima per titolo e abstract, poi per intero. La valutazione della qualità è stata effettuata utilizzando la Newcastle-Ottawa Quality Assessment Scale (NOS).

Risultati. Sono stati trovati 28 articoli, di cui soltanto 4 sono stati inclusi in questa revisione. Questi studi sono stati condotti in Francia, Svizzera, Stati Uniti e Germania. Essi hanno mostrato interessanti evidenze cliniche su come questa micosi multiresistente interumana possa facilmente diventare una malattia infettiva epidemica a trasmissione sessuale.

Conclusioni. Questa revisione sistematica sottolinea come la diffusione di questo patogeno, genotipo VII, nell'uomo non debba essere sottovalutata. Di conseguenza, per facilitare un intervento precoce ed evitare una crescita epidemica multiresistente di questa infezione, sono necessarie nuove modalità diagnostiche.

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