Review

Paracoccidioidomycosis Diagnosed in Europe—A Systematic Literature Review

Gernot Wagner 1,*, Deddo Moertl 2, Anna Glechner 1, Verena Mayr 1, Irma Klerings 1, Casey Zachariah 1, Miriam Van den Nest 3,4, Gerald Gartlehner 1,5 and Birgit Willinger 4

1 Department for Evidence-based Medicine and Evaluation, Danube University Krems, Dr.-Karl-Dorrek-Strasse 30, 3500 Krems, Austria; anna.glechner@donau-uni.ac.at (A.G.); verena.mayr@donau-uni.ac.at (V.M.); irma.klerings@donau-uni.ac.at (I.K.); Casey.Zachariah@hotmail.com (C.Z.); gerald.gartlehner@donau-uni.ac.at (G.G.)
2 Clinical Department of Internal Medicine III, University Hospital St. Poelten, Karl Landsteiner University of Health Sciences, Dunant-Platz 1, 3100 St. Poelten, Austria; deddo.moertl@stpoelten.lknoe.at
3 Department for Infection Control and Hospital Epidemiology, Medical University of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria; miriam.vandennest@meduniwien.ac.at
4 Division of Clinical Microbiology, Department of Laboratory Medicine, Medical University of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria; birgit.willinger@meduniwien.ac.at
5 RTI International, 3040 East Cornwallis Road, P.O. Box 12194, Research Triangle Park, NC 27709-2194, USA
* Correspondence: gernot.wagner@donau-uni.ac.at; Tel.: +43-2732-893-2913

Abstract: Paracoccidioidomycosis is a systemic mycosis that is endemic in geographical regions of Central and South America. Cases that occur in nonendemic regions of the world are imported through migration and travel. Due to the limited number of cases in Europe, most physicians are not familiar with paracoccidioidomycosis and its close clinical and histopathological resemblance to other infectious and noninfectious disease. To increase awareness of this insidious mycosis, we conducted a systematic review to summarize the evidence on cases diagnosed and reported in Europe. We searched PubMed and Embase to identify cases of paracoccidioidomycosis diagnosed in European countries. In addition, we used Scopus for citation tracking and manually screened bibliographies of relevant articles. We conducted dual abstract and full-text screening of references yielded by our searches. To identify publications published prior to 1985, we used the previously published review by Ajello et al. Overall, we identified 83 cases of paracoccidioidomycosis diagnosed in 11 European countries, published in 68 articles. Age of patients ranged from 24 to 77 years; the majority were male. Time from leaving the endemic region and first occurrence of symptoms considerably varied. Our review illustrates the challenges of considering systemic mycosis in the differential diagnosis of people returning or immigrating to Europe from endemic areas. Travel history is important for diagnostic-workup, though it might be difficult to obtain due to possible long latency period of the disease.

Keywords: paracoccidioidomycosis; Paracoccidioides spp.; endemic systemic mycosis

1. Introduction

Paracoccidioidomycosis, also known as South American blastomycosis, is a systemic fungal infection [1] caused by the thermally dimorphic fungi of the species Paracoccidioides brasiliensis and the related species P. americana, P. restrepiensis, P. venezuelensis, and P. lutzii [2,3]. These fungi are endemic to certain geographic regions of Central and South America [4]. Most of the cases of paracoccidioidomycosis are reported in Brazil, followed by Colombia, Venezuela, Ecuador, and Argentina [5]. Based on estimates from epidemiological data, the number of cases of paracoccidioidomycosis in Brazil ranges from 3360 to 5600 per year [5]. The incidence of cases considerably varies among regions with low, moderate
or high endemicity [5]. According to estimates, in regions with a stable endemic situation, the annual incidence of paracoccidioidomycosis ranges from 1 to 4 cases per 100,000 inhabitants [5].

People living in rural areas and working in agriculture are particularly at risk for this mycosis [1]. The risk of infection is higher for men than women [6]. The chronic form (adult type) accounts for the majority of cases [4]. This form of paracoccidioidomycosis is progressive over months or years and can be unifocal, if only one site is affected, or multifocal, in case of dissemination [7]. The organ most frequently affected is the lung [7]. Skin, oral mucosa, pharynx, larynx, lymph nodes, adrenal glands, central nervous system, bones, or joints may also be affected [8]. Symptoms of the disease can be systemic (e.g., weight loss, general weakness) or related to specific organ affection (e.g., cough, shortness of breath) [8]. In particular, pulmonary affection, lymphadenopathy, and B symptoms often lead to clinical signs similar to tuberculosis [8,9].

Paracoccidioidomycosis differential diagnosis is particularly challenging, because clinical signs and symptoms, as well as histopathological findings, resemble numerous other infections (e.g., tuberculosis) and noninfectious diseases (e.g., sarcoidosis) [8]. In addition, a long latency period [7] between exposure and manifestation of symptoms, as well as limited clinical experience, make adequate diagnosis difficult. In nonendemic areas, the history of travel and residency in endemic regions is a key to consider paracoccidioidomycosis for differential diagnosis.

Most physicians in nonendemic areas are unfamiliar with the clinical picture of endemic systemic mycoses because they are rarely presented to them. This in turn increases the risk that patients with paracoccidioidomycosis end up with misdiagnosis or remain undiagnosed. Subsequently, this results in no or inappropriate therapy. Therefore, it is important to provide information about the disease presentations in nonendemic regions. A previously published review by Ajello et al. 1985 [10] comprehensively summarized internationally published cases of paracoccidioidomycosis from Africa, Asia, the Middle East, North America, and Europe [10]. However, this review is now 35 years old and needs to be updated.

The purpose of this systematic review is to summarize the evidence of paracoccidioidomycosis imported to nonendemic European countries. Thereby, we aim to increase awareness for this fungal infection and provide important information regarding its challenging diagnosis.

2. Materials and Methods

For reporting of this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [11].

2.1. Information Sources and Literature Search

An experienced information specialist searched PubMed and Embase (Embase.com) from inception to June 15 and 16, 2020 to identify relevant publications. We used a combination of subject headings and title and abstract free-text terms. We restricted our search to adults and humans. We have provided the detailed search strategy in Appendix A (Tables A1 and A2). In addition to database searches, we used Scopus (Elsevier) on June 16, 2020 to perform forward and backward citation tracking of included publications and reviews. We also manually screened reference lists of these records, in case the reference lists available via Scopus were incomplete. To identify publications published prior to 1985, we used the previous review published by Ajello et al. [10]. We used references found by our search to identify relevant publications published in 1985 or later.
2.2. Eligibility Criteria and Study Selection

Our population of interest was adults of any age and origin diagnosed with paracoccidioidomycosis (South American blastomycosis) in geographic Europe. We considered any case description of an acute or chronic form of paracoccidioidomycosis as eligible for this review if authors provided sufficient clinical information on number of cases, country of exposure, and diagnosis. Publications were included regardless of language and type of publication. We included case series and case reports, observational studies, reviews providing information mentioned above and published as abstracts, full-articles, letters, and editorials. Table 1 provides a summary of eligibility criteria.

After a pilot round, two reviewers independently screened each title and abstract. Eligible publications subsequently underwent independent dual full-text assessment. We solved disagreements by consensus or involvement of a senior reviewer. Throughout the whole study selection process, we used the web-based software Covidence [12]. We organized search and screening results in an EndNote® X9 bibliographic database (Clarivate, Pennsylvania, USA).

| Table 1. Eligibility criteria. |
|-------------------------------|
| **Inclusion**                  | **Exclusion**                  |
| Population                     |                                |
| Adults of any age and origin   | Children and adolescents       |
| Diagnosed with acute or chronic form of paracoccidioidomycosis (South American blastomycosis) | Any other infections |
| Sufficient clinical information on number of cases, country of exposure and diagnosis | Insufficient clinical information |
| Region                         | Diagnosis was made outside geographic Europe |
| Diagnosis was made in geographic Europe |                                |
| Case reports and case series   |                                |
| Study design                   |                                |
| Observational studies          | Reviews                        |
| Publication type               | Any (e.g., abstract, full article, letters, and editorials) |
| Language                       | Any                            |

2.3. Data Collection Process and Evidence Synthesis

We extracted the following relevant information from each article into pilot-tested evidence tables: author, year, study design, language, country of diagnosis, country of exposure, number of cases, patient characteristics (age, gender, occupation, affected organ(s), systemic antymycotic therapy, and treatment response), and latency period. If the publication language was not English, we asked native speakers to translate or used the online tool DeepL (http://www.deepl.com (accessed on 15 January 2021)) for translations into German. We synthesized data of identified articles narratively.

3. Results

3.1. Study Selection and Characteristics

Overall, we identified 83 case reports from 11 European countries, published in 68 articles. Figure 1 shows details of the study selection process.
Table 2 summarizes the number of publications and reported cases by country. Spain reported most of the cases, followed by Italy and Germany. The majority of articles were written in English or Spanish. Other publication languages were German, Portuguese, Italian, Norwegian and French.

Table 2. Number of identified publications and reported cases of paracoccidioidomycosis by country of diagnosis.

| Country of Diagnosis | No. of Publications | No. of Reported Cases |
|----------------------|---------------------|-----------------------|
| Austria              | 2                   | 2                     |
| Bulgaria             | 1                   | 1                     |
| France               | 5                   | 5                     |
| Germany              | 8                   | 9                     |
| Great Britain        | 5                   | 6                     |
| Italy                | 15                  | 15                    |
| Netherlands          | 1                   | 1                     |
| Norway               | 1                   | 1                     |
| Portugal             | 7                   | 7                     |
| Spain                | 21                  | 35 \(^1\)             |
| Switzerland          | 2                   | 1                     |
| **Total**            | **68**              | **83**                |

\(^1\) Based on number of cases reported by Vivancos et al. 1969 [13] \((n = 1)\), Pereiro Miguens et al. 1974 [14] \((n = 2)\), Simon Merchán, et al. 1970 [15] \((n = 1)\), Pereiro Miguens et al. 1987 [16] \((n = 1)\), Miguélez et al. 1995 [17] \((n = 2)\), Molina-Morant et al. 2018 [18] \((n = 25)\), Agirre et al. 2019 [19] \((n = 2)\) and Chamorro-Tojeiro et al. 2020 [20] \((n = 1)\). Abbreviation: No., number; \(n\), number of patients.

### 3.2. Clinical Patient Characteristics

The age of the patients ranged from 24 to 77 years. The infection mainly affected men. In most cases, exposure to Paracoccidioides took place in Venezuela, followed by Brazil and Ecuador. The most common occupations were field and construction workers. Latency period, defined as the period from leaving the endemic region until occurrence of first symptoms or medical contact, ranged from six days to 50 years. Table 3 shows patient
characteristics, country of exposure, latency period, affected organ(s), systemic antymycotic therapy and response to treatment grouped by countries in which the diagnosis was made.
Table 3. Imported cases of paracoccidioidomycosis from Central and South America diagnosed in Europe.

| Author, Year | Study Design Language | No. of Cases | Age Years, Gender | Suspected Country of Exposure | Latency Period 1 | Occupation | Affected Organ(s) | Systemic Antimycotic Therapy | Treatment Response |
|--------------|-----------------------|--------------|-------------------|-------------------------------|-----------------|-----------|------------------|-----------------------------|-------------------|
| Austria      |                        |              |                   |                               |                 |           |                  |                             |                   |
| Wagner et al. 2016 [21] | Case report English | 1 | 62, M | Peru | 6 years | Construction worker | Adrenal glands, brain, lung, lymph node | Amphotericin B, itraconazole, posaconazole | Clinical improvement during hospital stay |
| Mayr et al. 2004 [22] | Case report English | 1 | 43, F | Brazil, Venezuela, or Mexico | 4 years | Government employee | Lung, lymph node | Amphotericin B, voriconazole | Clinical improvement |
| Bulgaria     |                        |              |                   |                               |                 |           |                  |                             |                   |
| Balabanov et al. 1964 [23] | Case report * French | 1 | 67, M | Brazil | 30 years | Worked in the jungle | Lung, oral mucosa | Sulfonamide, trimethoprim | Complete remission |
| Germany      |                        |              |                   |                               |                 |           |                  |                             |                   |
| Kayser et al. 2019 [24] | Case report English | 1 | 57, F | Venezuela | 1 year | NR | Lung | Amphotericin B, itraconazole | Clinical improvement during hospital stay, remained under control |
| Slevogt et al. 2004 [25] | Case report English | 1 | 31, F | Brazil | 10 years | NR | Lymph nodes | Itraconazole | Complete remission |
| Horré et al. 2002 [26] | Case report English | 1 | 61, M | Brazil | 10 years | Legionnaire | Lung, oral mucosa, skin | Itraconazole | Complete remission |
| Köhler et al. 1988 [27] | Case report German | 1 | 49, M | Brazil | 15 years | Gold mine worker | Brain, lung, oral and laryngeal mucosa | Amphotericin B, ketoconazole, itraconazole | Clinical improvement during hospital stay, remained under control |
| Study                        | Type               | Country | Age (years) | Sex | Location          | Disease Manifestations                                                                 | Therapy          | Outcomes                      |
|------------------------------|--------------------|---------|-------------|-----|-------------------|----------------------------------------------------------------------------------------|------------------|-------------------------------|
| Neveling 1988 [28]           | Case series        | Germany | 64          | M   | Brazil            | Lung, none                                                                              | None             | Clinical improvement, remained under control |
| Neveling 1988 [28]           | Case series        | Germany | 64          | M   | Brazil            | Lung, none                                                                              | None             | Clinical improvement, remained under control |
| Braeuninger et al. 1985 [29], Hastra et al. 1985 [30] | Case report        | German  | 32          | M   | Peru              | Lung, lymph nodes, oral mucosa, skin                                                   | Ketoconazole     | Clinical improvement          |
| Altmeyer 1976 [31]           | Case report *      | German  | 69          | M   | Paraguay          | Lung, lymph nodes, oral mucosa, skin                                                   | Imidazole        | Patient deceased              |
| PORTUGAL                     |                    |         |             |     |                   |                                                                                         |                  |                               |
| Ferreira et al. 2017 [32]    | Case report        | Portuguese | 46        | M   | Brazil            | Lung, lymph nodes, oral mucosa                                                          | Itraconazole     | Clinical improvement          |
| Coelho et al. 2013 [33]      | Case report (Abstract only) | English | 63          | M   | Brazil            | Oral and pharyngeal mucosa                                                              | NR               | NR                            |
| Alves et al. 2013 [34]       | Case report        | Portuguese | 43        | M   | Venezuela         | Lung, oral mucosa, skin                                                                  | Itraconazole     | Complete remission            |
| Armas et al. 2012 [35]       | Case report        | English  | 43          | M   | Venezuela         | Lung, skin                                                                              | Itraconazole     | Clinical improvement          |
| Carvalho et al. 2009 [36]    | Case report        | Portuguese | 24        | M   | Brazil            | Construction worker                                                                     | Itraconazole     | Clinical improvement          |
| Villar et al. 1963 [37]      | Case report **     |         | -           |     | Brazil            | -                                                                                       | -                |                               |
| Oliveira et al. 1960 [38]    | Case report **     | Portuguese | -          |     | Brazil            | -                                                                                       | -                |                               |
| SPAIN                        |                    |         |             |     |                   |                                                                                         |                  |                               |
| Study                          | Type                          | Country  | Age  | Sex | Duration | Location          | Treatment                  | Outcome                                      |
|-------------------------------|-------------------------------|----------|------|-----|----------|-------------------|-----------------------------|----------------------------------------------|
| Chamorro-Tojeiro et al. 2020  | Case report English           | Mexico   | 42   | M   | 6 days   | Lung              | Itraconazole                | Complete remission, remained under control   |
| Agirre et al. 2019 [19]       | Case series English           | Peru     | 29   | F   | 10 days  | Lung, lymph nodes | Itraconazole                | Complete remission                       |
|                               |                               |          | 31   | M   | 10 days  | Lung              | Itraconazole                | Complete remission                       |
| Molina-Morant et al. 2018 [18]| Retrospective observational study English |          | Median 48 yrs (range 33 to 67), M 16 (64%) | This retrospective study reported 25 cases of paracoccidioidomycosis admitted to Spanish hospitals between 1 January 1997 to 31 December 2014. |
| Navascués et al. 2013 [39]    | Case report Spanish           | Ecuador  | 47   | M   | 11 years | Lung, lymph nodes, skin | Amphotericin B, itraconazole | Complete remission                       |
|                               |                               |          | 67   | M   |          | Lung              | Amphotericin B, itraconazole | Complete remission                       |
|                               |                               |          | 57   | M   |          | NR                | NR                          | Complete remission                       |
|                               |                               |          | 44   | M   |          | NR                | NR                          | Complete remission                       |
|                               |                               |          | 51   | M   |          | NR                | NR                          | Complete remission                       |
|                               |                               |          | 31   | M   |          | NR                | NR                          | Complete remission                       |
|                               |                               |          | NR   | M   |          | NR                | NR                          | Complete remission                       |
| Buitrago et al. 2011 [40]     | Case series English           | Paraguay | 48   | M   | 6 years  | Lung              | Itraconazole                | Complete remission                       |
|                               |                               |          | 56   | M   | 6 months | Lung              | Itraconazole, amphotericin B | Complete remission                       |
| Ramírez-Olivencia et al. 2010 | Case report English           | Paraguay | 43   | M   | NR       | Lung              | Itraconazole                | Clinical improvement; disappearance of oral and laryngeal lesions |
| Botas-Velasco et al. 2010 [43]| Case report Spanish           | Ecuador  | 63   | M   | 8 months | Lung              | Itraconazole                | Patient deceased                          |
| Mayayo et al. 2007 [44]       | Case report English           | Ecuador  | 27   | M   | None     | Lymph nodes, skin | Itraconazole                | Complete remission                       |
| López Castro et al. 2005 [45] | Case report Spanish           | Venezuela| 63   | M   | 8 months | Lung, skin        | Amphotericin B              | Patient deceased                         |
| Authors                  | Type            | Country | Age | Sex  | Disease Sites                | Treatment               | Outcome                  |
|-------------------------|-----------------|---------|-----|------|------------------------------|-------------------------|--------------------------|
| Ginarte et al. 2003     | Case series     | Venezuela | 50 years | NR | Skin                       | Fluconazole             | Remained under control   |
|                         | English         |         |     |      |                              |                         |                          |
|                         |                 | 67, M   | Brazil | 1 year | Oral mucosa, teeth          | Itraconazole, sulfonamides | Complete remission       |
|                         |                 | 65, M   | Venezuela | 38 years | Oral mucosa                | Fluconazole             | Remained under control   |
| Garcia Bustínduy et al. | Case report     | Venezuela | 1 year | Taxi driver | Skin                       | Itraconazole             | Complete remission       |
| 2000                    | English         |         |     |      |                              |                         |                          |
| Del Pozo et al. 1998    | Case report     | Venezuela | 13 years | NR | Lung, oral and nasal mucosa | Itraconazole             | Complete remission       |
|                         | Spanish         |         |     |      |                              |                         |                          |
| Garcia et al. 1997      | Case report     | Venezuela | 50 years | NR | Lung, oral mucosa, skin     | Fluconazole             | Complete remission       |
|                         | Spanish         |         |     |      |                              |                         |                          |
| Pereiro et al. 1996     | Case report     | Venezuela | NR | NR |                              |                         | This case was also described by Ginarte et al. 2003 and is therefore not presented here again. |
|                         | English         |         |     |      |                              |                         |                          |
| Miguélez et al. 1995    | Case report     | Venezuela | 2 years | NR | Brain, lung, lymph nodes    | Itraconazole             | Patient deceased (tuberculosis coinfection) |
|                         | Spanish         |         |     |      |                              |                         |                          |
|                         |                 | 53, M   | Venezuela | 18 months | Lung, lymph nodes, oral mucosa | Itraconazole            | Clinical improvement     |
| Pereiro Miguens et al.  | Case report     | Venezuela | 23 years | Construction worker | Oral mucosa, skin | Ketoconazole             | Clinical improvement     |
| 1987                    | Spanish         |         |     |      |                              |                         |                          |
| Simon Merchán et al. 1970 | Case report ** | Venezuela | 2 years | - | -                           | -                       | -                        |
| Pereiro Miguens et al.  | Case report *   | Venezuela | 7 years | NR | Lung, oral mucosa           | Sulfonamide, trimethoprim | Clinical improvement     |
| 1974, Pereiro Miguens   | Spanish         |         |     |      |                              |                         |                          |
|                         | Case report      |         |     |      |                              |                         |                          |
|                         |                  | 44, M   | Venezuela | 8 years | Oral mucosa                | Sulfonamide, trimethoprim | Clinical improvement     |
|                         |                  | 49, M   | Venezuela | 8 years | Oral mucosa                | Sulfonamide, trimethoprim | Clinical improvement     |
| Author(s)         | Year | Gender | Age | Nationality | Occupation          | Site(s)                                 | Treatment                        | Outcome                                    |
|------------------|------|--------|-----|-------------|---------------------|-----------------------------------------|------------------------------------|--------------------------------------------|
| Vivancos et al.  | 1969 | 44 M   |     | Venezuela   | Farmer              | Oral mucosa                            | Sulfamethoxazole / trimethoprim, amphotericin B | Complete remission                      |
| De Cordova et al.| 2012 | 52 M   |     | Venezuela   | Butcher             | Oral mucosa                            | Itraconazole                       | Complete remission                      |
| Sierra et al.    | 2011 | 77 M   |     | Ecuador     | NR                  | Lung, lymph nodes, oral mucosa, skin   | Itraconazole                       | NR                                        |
| Walker et al.    | 2008 | 51 M   |     | Venezuela   | None                | Lung, oral mucosa, skin                | Itraconazole                       | Clinical improvement, cutaneous lesions cleared |
| Bowler et al.    | 1986 | 57 F   | 17 years | Argentina, Venezuela | Clerk | Lung | NR | NR |
| Symmers 1966     |      | 42 M   |     | Brazil      | NR                  | Skin                                   | NR No therapy                      | Patient deceased (acute heart failure)    |
| Borgia et al.    | 2000 | 61 M   |     | Venezuela   | House-painter       | Bones, lung                            | Itraconazole                       | Clinical improvement                     |
| Pecoraro et al.  | 1998 | 60 M   |     | Venezuela   | Coffee plantations worker | Bones, lung                            | Ketoconazole                       | Clinical improvement                     |
| Solaroli et al.  | 1998 | 49 M   |     | Brazil      | NR                  | Brain, lung, skin                      | Itraconazole                       | Clinical improvement                     |
| Authors            | Year   | Country  | Age | Gender | Duration of Disease | Occupation | Symptoms                                      | Treatment                      | Outcome                      |
|--------------------|--------|----------|-----|--------|---------------------|------------|-----------------------------------------------|-------------------------------|------------------------------|
| Fulciniti et al.   | 1996   | Venezuela| 60, M | NR     | NR                  | Bones, lung| Itraconazole                                  | Clinical improvement, remained under control |
| Cuomo et al.       | 1985   | Venezuela| 37, M | 2 years | Butcher             | Lung, skin | Ketoconazole                                  | Clinical improvement          |
| Benoldi et al.     | 1985   | Venezuela| 41, M | Few months | Butcher         | Lung, lymph nodes, skin | Ketoconazole, sulfamethoxy-pyridazine | Complete remission           |
| Cuomo et al.       | 1985   | Venezuela| 37, M | 2 years | Butcher             | Lung, skin | Ketoconazole                                  | Clinical improvement          |
| Benoldi et al.     | 1985   | Venezuela| 41, M | Few months | Butcher         | Lung, lymph nodes, skin | Ketoconazole, sulfamethoxy-pyridazine | Complete remission           |
| Finzi et al.       | 1980   | Brazil   | 14 years | -       | -                  | -           | -                                             | -                            |
| Vellutti et al.    | 1979   | Venezuela| 52, M | 17 years | Fabric retailer    | Lung       | Amphotericin B, miconazole                    | Clinical improvement          |
| Lasagni et al.     | 1979   | Venezuela| NR   | -       | -                  | -           | -                                             | -                            |
| Scarpa et al.      | 1965   | Venezuela| 43, M | 5 years | Farmer             | Lung, oral mucosa, skin | Amphotericin B, sulfamethoxazole            | Patient deceased              |
| Schiralde et al.   | 1963   | Venezuela| None  | -       | -                  | -           | -                                             | -                            |
| Molese et al.      | 1956   | Venezuela| 47, M | None    | Painter            | Lung, lymph nodes, oral mucosa | Nystatin                           | NR                           |
| Farris 1955        |        | Brazil   | 7 years | -       | -                  | -           | -                                             | -                            |
| Bertacini 1934     |        | Brazil   | None  | -       | -                  | -           | -                                             | -                            |
| Dalla Favera 1914  |        | Brazil   | None  | -       | -                  | -           | -                                             | -                            |
| FRANCE             |        |          |       |         |                     |             |                                               |                               |
| Heleine et al.     | 2020   | Brazil   | 48, M | NR     | Farmer             | Lung, lymph nodes, oropharyngeal mucosa, skin | Itraconazole                    | Clinical improvement          |
| Author(s) | Type | Language | Gender | Age | Location | Latency | Occupation | Lesions | Treatment | Clinical Improvement |
|----------|------|----------|--------|-----|----------|---------|------------|---------|-----------|----------------------|
| Dang et al. 2017 [73] | Case report | English | 54, M | 12 years | Columbia, Venezuela | Itraconazole | Clinical improvement; almost complete resolution of the tongue lesion and lymphadenopathy |
| Sambourg et al. 2014 [74] | Case report | French | 43, M | NR | Brazil | NR | Skin | NR | NR |
| Laccourreye et al. 2010 [75] | Case report | English | 46, M | NR | Venezuela | Engineer | Laryngeal mucosa | Itraconazole | Complete remission |
| Poisson et al. 2007 [76] | Case report | English | 70, M | 6 years | Paraguay | NR | Brain, lung | Fluconazole, Itraconazole | Remained clinically stable |
| Van Damme et al. 2006 [77] | Case report | English | 60, M | 8 years | Peru, Ecuador | Carpenter | Lung, oral mucosa, urinary tract | Itraconazole | Clinical improvement, remained under control |
| Maehlen et al. 2001 [78] | Case report | Norwegian | 51, F | 23 years | Brazil | NR | Brain | - | Patient deceased |
| Stanisic et al. 1979 [79], Wegmann et al. 1959 [80] | Case report | German | 47, M | 5 years | Brazil | Carpenter | Lung, lymph nodes, oral mucosa | Hydroxy-stilbamidine, amphotericin B, sulfonamide | Patient deceased (Cor pulmonale) |

**Abbreviations:** M, male; F, female; NR, not reported; yrs, years; † Latency period from leaving the endemic region until occurrence of first symptoms or medical contact; ‡ We assume that most of 25 cases diagnosed in Spain between 1997 to 2014 and published by Molina-Morant et al. 2018 [18] are also described in case reports and case series presented in this table; * Included in the review by Ajello et al. 1985 [10]; ** Included in the review by Ajello et al. 1985, full-text not available, data extracted from Ajello et al. 1985 [10].
3.3. Differential Diagnosis

Table A3 of Appendix A shows infectious and non-infectious diseases that were considered for differential diagnosis of cases in the included articles.

3.4. Diagnostic Work-Up

The diagnostic workup varied across publications. Usually, *Paracoccidioides* spp. was identified from clinical specimens through microscopic visualization and/or culture. In addition, some of the authors reported results from serological tests and/or molecular biological techniques such as polymerase chain reaction (PCR). Table A3 provides information on diagnostic workup in individual cases of paracoccidioidomycosis.

In general, direct examination, using 10% potassium hydroxide applied to different samples, is effective and inexpensive. A histologic examination of tissue specimens using silver methenamine or periodic acid–Schiff stain is common and practical when patients present with oral or other skin lesions. In a clinical sample, *Paracoccidioides* spp. appear as globose yeast cells with multiple buds and a thick refractile wall [81].

4. Discussion

Our systematic review summarizes the evidence on published case reports of imported paracoccidioidomycosis diagnosed in Europe. To the best of our knowledge, this is the most recent and comprehensive review of published cases of this systematic mycosis endemic to geographical regions of Central and South America. While narrative reviews on patients with this disease often included a nonsystematic search, we followed a systematic approach with a much broader scope to identify all published cases of paracoccidioidomycosis imported to Europe. In addition, the last systematic assessment of case reports on paracoccidioidomycosis was published in 1985, almost four decades ago [10]. A more recent narrative review focused only on cases diagnosed in Spain [82].

Our systematic review of case reports and case series emphasizes the clinical challenges and pitfalls of paracoccidioidomycosis. Most of the physicians in non-endemic regions such as Europe are unfamiliar with systemic mycosis. They struggle with the diagnostic work-up and management due to several reasons. In general, depending on the type, clinical presentation of patients with paracoccidioidomycosis is variable [4]. A major issue is the clinical similarity to several other infectious and non-infectious diseases [81]. Paracoccidioidomycosis is commonly misdiagnosed as tuberculosis [83]. The clinical picture of tuberculosis resembles the chronic progressive form of paracoccidioidomycosis [9].

The differential diagnosis of chronic paracoccidioidomycosis with lung involvement also includes coccidioidomycosis, histoplasmosis, sarcoidosis, pneumoconiosis, interstitial pneumonia, and malignancy [84]. Inappropriate treatment could have harmful consequences for the patient, without any prognostic impact on systemic mycosis. In addition, the latency period from pathogen exposure to development of symptoms is highly variable and might comprise several decades when patients might already have left the endemic region [7]. Therefore, clinicians must inquire about any short- and long-term stay (travel and residency) in endemic areas and even time abroad many years preceding presentation. Figure 2 summarizes important aspects that have to be considered for diagnosis of paracoccidioidomycosis, including signs and symptoms, travel history, and imaging.
If paracoccidioidomycosis is considered for differential diagnosis, clinicians should provide this information to the microbiologist, pathologist and other laboratory personnel to ensure that adequate methods for direct and indirect identification of the pathogen are applied. In addition, laboratory personnel need to apply safety precautions when collected specimens are handled.

The strengths of our work are the systematic literature search and screening. However, this systematic review has several limitations. First, we have not included cases that may have been diagnosed but never published. Second, because translation methods varied, we might have missed relevant information in the articles. A native speaker translated Spanish texts into German but online electronic translation tools provided translations for all other languages (11 publications) except texts published in English and German. Third, our findings rely on not uniformly structured case reports and cases series that are considered as low-level evidence. Finally, although we conducted comprehensive additional literature searches, we might have missed studies not cited in previous reviews and not indexed in electronic databases due to very early publication dates or non-indexed journals.

5. Conclusions

In conclusion, this review highlights the importance of considering systemic mycosis in the differential diagnosis of people with symptoms of tuberculosis who have either returned to Europe from endemic areas or were natives of endemic countries who migrated to Europe. In light of systemic mycosis’s potentially long latency period, extensive evaluation of travel history is an essential key for a quick and correct diagnosis of systemic endemic mycosis such as paracoccidioidomycosis.

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List of Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| PCR          | polymerase chain reaction |
| PCM          | paracoccidioidomycosis |
| PRISMA       | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |

Appendix A

Table A1. Search Strategy Pubmed 15 June 2020.

| Search Number | Query                                                                 | Results |
|---------------|-----------------------------------------------------------------------|---------|
| 1             | “Paracoccidioidomycosis”[Mesh]                                        | 1833    |
| 2             | Paracoccidioidomycos*[tiab]                                           | 1782    |
| 3             | Paracoccidioides brasiliensis*[tiab]                                  | 1611    |
| 4             | paracoccidioidal granuloma*[tiab]                                     | 9       |
| 5             | South american blastomycosis*[tiab]                                   | 272     |
| 6             | #1 OR #2 OR #3 OR #4 OR #5                                            | 2858    |
| 7             | “Europe”[Mesh]                                                       | 1,408,827 |
| 8             | “Emigrants and Immigrants”[Mesh]                                      | 12,277  |
| 9             | “Travel”[Mesh:NoExp]                                                 | 24,916  |
| 10            | (Albania*[tiab] OR Andorra*[tiab] OR Armenia*[tiab] OR Austria*[tiab] OR Azerbaijan*[tiab] OR Belarus*[tiab] OR Belgi*[tiab] OR Bosnia*[tiab] OR Herzegov*[tiab] OR Bulgaria*[tiab] OR Croatia*[ad] OR Cypr*[ad] OR Czech*[ad] OR Denmark*[ad] OR danish*[ad] OR Estonia*[ad] OR Finland*[ad] OR finnish*[ad] OR France*[ad] OR french*[ad] OR Georgia*[ad] OR German*[ad] OR Greece*[ad] OR greek*[ad] OR Hungar*[ad] OR Iceland*[ad] OR Ireland*[ad] OR irish*[ad] OR Italy*[ad] OR Italian*[ad] OR Kazak*[ad] OR Kosov*[ad] OR Latvia*[ad] OR Liechtenstein*[ad] OR Lithuania*[ad] OR Luxembourg*[ad] OR Macedon*[ad] OR Malat*[ad] OR malese*[ad] OR Moldov*[ad] OR Monac*[ad] OR Montenegr*[ad] OR Netherlands*[ad] OR dutch*[ad] OR Norway*[ad] OR norwegian*[ad] OR Poland*[ad] OR polish*[ad] OR Portug*[ad] OR Romanian*[ad] OR Russian*[ad] OR San Marino*[ad] OR Serbia*[ad] OR Slovak*[ad] OR Slovenia*[ad] OR Spain*[ad] OR spanish*[ad] OR Sweden*[ad] OR swedish*[ad] OR Switzerland*[ad] OR swiss*[ad] OR Turkey*[ad] OR turkish*[ad] OR Ukran*[ad] OR United Kingdom*[ad] OR britain*[ad] OR british*[ad]) | 1,082,126 |
| 11            | (Albania*[ad] OR Andorra*[ad] OR Armenia*[ad] OR Austria*[ad] OR Azerbaijan*[ad] OR Belarus*[ad] OR Belg*[ad] OR Bosnia*[ad] OR Herzegov*[ad] OR Bulgaria*[ad] OR Croatia*[ad] OR Cypr*[ad] OR Czech*[ad] OR Denmark*[ad] OR danish*[ad] OR Estonia*[ad] OR Finland*[ad] OR finnish*[ad] OR France*[ad] OR french*[ad] OR Georgia*[ad] OR German*[ad] OR Greece*[ad] OR greek*[ad] OR Hungar*[ad] OR Iceland*[ad] OR Irish*[ad] OR Italian*[ad] OR Kazak*[ad] OR Kosov*[ad] OR Latvia*[ad] OR Liechtenstein*[ad] OR Lithuania*[ad] OR Luxembourg*[ad] OR Macedon*[ad] OR Malat*[ad] OR Malese*[ad] OR Moldov*[ad] OR Monac*[ad] OR Montenegr*[ad] OR Netherlands*[ad] OR dutch*[ad] OR Norway*[ad] OR norwegian*[ad] OR Poland*[ad] OR polish*[ad] OR Portug*[ad] OR Romanian*[ad] OR Russian*[ad] OR San Marino*[ad] OR Serbia*[ad] OR Slovak*[ad] OR Slovenia*[ad] OR Spain*[ad] OR Spanish*[ad] OR Sweden*[ad] OR swedish*[ad] OR Switzerland*[ad] OR swiss*[ad] OR Turkey*[ad] OR turkish*[ad] OR Ukran*[ad] OR United Kingdom*[ad] OR britain*[ad] OR british*[ad]) | 5,875,438 |
| 12            | europ*[tiab] OR immigrant*[tiab] OR travel*[tiab]                       | 383,712 |
| No. | Query                                                                 | Results |
|-----|-----------------------------------------------------------------------|---------|
| 13  | non endemic[tiab] OR nonendemic[tiab]                                | 4492    |
| 14  | #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7                          | 7,173,281|
| 15  | #6 AND #14                                                           | 204     |
| 16  | (“Animals”[Mesh] NOT “Humans”[Mesh])                                 | 4,707,502|
| 17  | #15 NOT #16                                                          | 175     |

Table A2. Search Strategy Embase 16 June 2020.

| No.  | Query                                                                 | Results |
|------|-----------------------------------------------------------------------|---------|
| 1    | ‘south american blastomycosis’/exp OR ‘paracoccidioides brasiliensis’/exp | 3026    |
| 2    | paracoccidioidomycos*:ab,ti OR ‘paracoccidioides brasiliensis’:ab,ti OR ‘paracoccidioidal granuloma’:ab,ti | 3075    |
| 3    | #1 OR #2                                                              | 3620    |
| 4    | ‘europe’/exp OR ‘immigrant’/exp OR ‘travel’/exp                       | 1,695,885|
|      | albania*:ca,ab,ti OR andorra*:ca,ab,ti OR armenia*:ca,ab,ti OR austria*:ca,ab,ti OR azerbaijan*:ca,ab,ti OR belarus*:ca,ab,ti OR belgi*:ca,ab,ti OR bosnia*:ca,ab,ti OR herzegov*:ca,ab,ti OR bulgaria*:ca,ab,ti OR croatia*:ca,ab,ti OR cypr*:ca,ab,ti OR czech:ca,ab,ti OR danmark:ca,ab,ti OR danish:ca,ab,ti OR estonia*:ca,ab,ti OR finland:ca,ab,ti OR finnish:ca,ab,ti OR france:ca,ab,ti OR french:ca,ab,ti OR georgia*:ca,ab,ti OR german*:ca,ab,ti OR greece:ca,ab,ti OR hungary*:ca,ab,ti OR iceland*:ca,ab,ti OR ireland:ca,ab,ti OR irish:ca,ab,ti OR italy:ca,ab,ti OR italian:ca,ab,ti OR kazak*:ca,ab,ti OR kosov*:ca,ab,ti OR latvia*:ca,ab,ti OR liechtenstein*:ca,ab,ti OR lithuania*:ca,ab,ti OR luxembourg*:ca,ab,ti OR macedonia*:ca,ab,ti OR malta*:ca,ab,ti OR maltese*:ca,ab,ti OR moldov*:ca,ab,ti OR monac*:ca,ab,ti OR montenegro*:ca,ab,ti OR netherlands:ca,ab,ti OR dutch:ca,ab,ti OR norway:ca,ab,ti OR norwegian:ca,ab,ti OR poland:ca,ab,ti OR polish:ca,ab,ti OR portug*:ca,ab,ti OR portugal*:ca,ab,ti OR romania*:ca,ab,ti OR russia*:ca,ab,ti OR san marino*:ca,ab,ti OR serbia*:ca,ab,ti OR slovakia*:ca,ab,ti OR slovenia*:ca,ab,ti OR spain*:ca,ab,ti OR spanish*:ca,ab,ti OR sweden:ca,ab,ti OR swedish:ca,ab,ti OR switzerland:ca,ab,ti OR swiss:ca,ab,ti OR turkey*:ca,ab,ti OR turkish*:ca,ab,ti OR ukrain*:ca,ab,ti OR united kingdom*:ca,ab,ti OR britain*:ca,ab,ti OR british*:ca,ab,ti | 10,276,132|
| 5    | #14 OR #15 OR #16 OR #17                                             | 10,847,515|
| 6    | europ* OR ‘non endemic’ OR nonendemic OR travel*:ab,ti OR imported:ti | 2,203,591|
| 7    | immigrant*                                                           | 34,244  |
| 8    | #4 OR #5 OR #6 OR #7                                                 | 11,651,119|
| 9    | #3 AND #8                                                            | 457     |
| 10   | ‘animal’/exp NOT ‘human’/exp                                          | 5,449,241|
| 11   | #9 NOT #10                                                           | 405     |
| 12   | ‘groups by age’/exp NOT ‘adult’/exp                                   | 2,775,185|
| 13   | #11 NOT #12                                                          | 397     |
| 14   | ‘case report’/exp OR ‘case study’/exp OR ‘letter’/exp                | 3,471,553|
| 15   | case:ab,ti OR cases:ab,ti                                            | 4,628,697|
| 16   | ‘review’/exp OR ‘evidence based medicine’/exp                        | 3,575,830|
| 17   | review:ab,ti OR systematic:ab,ti OR search*:ab,ti OR ‘meta analy*’:ab,ti OR metaanaly*:ab,ti | 2,588,995|
| 18   | #14 OR #15 OR #16 OR #17                                             | 10,847,515|
| 19   | #13 AND #18                                                          | 256     |
| Author, Year          | Symptoms and Signs                                      | Differential Diagnosis       | Specimen for Histopathology                        | Histo-Logy 1 | Micro-Biology 2 | Sero-Logy | PCR |
|-----------------------|--------------------------------------------------------|------------------------------|--------------------------------------------------|--------------|----------------|-----------|-----|
| AUSTRIA               |                                                        |                              |                                                  |              |                |           |     |
| Wagner et al. 2016 [21]| Chest and abdominal pain, weight loss, night sweats, cough | Tuberculosis                | Left adrenal gland biopsy, extirpation of a right cervical lymph node | +            | +              | NR        | +   |
| Mayr et al. 2004 [22] | Cough, lymphadenopathy, weight loss                     | Tuberculosis, Wegener’s granulomatosis, sarcoidosis, mycosis | Lung biopsy                                      | +            | +              | +         | NR  |
| BULGARIA              |                                                        |                              |                                                  |              |                |           |     |
| Balabanov et al. 1964 [23]| Ulcerous oral and cutaneous lesions, lymphadenopathy | Tuberculosis                | Peribuccal lesion biopsy                         | +            | +              | NR        | NR  |
| GERMANY               |                                                        |                              |                                                  |              |                |           |     |
| Kayser et al. 2019 [24]| Cough, dyspnea                                         | Sarcoidosis, histoplasmosis | Lung biopsy                                      | +            | +              | +         | +   |
| Slevogt et al. 2004 [25]| Bilateral cervical and axillary lymphadenopathy, weight loss | Tuberculosis                | Cervical lymph node biopsy                        | +            | +              | NR        | NR  |
| Horré et al. 2002 [26]| Erythematous and swollen lips, mucocutaneous pustules and ulcerations, oral nodules, occasional night sweats | Leishmaniosis, tropical pulmonary mycosis, gammopathy | Oral lesion biopsy                               | +            | +              | +         | +   |
| Köhler et al. 1988 [27]| Cheilitis, erosive stomatitis, loss of teeth, dysphagia, aphonia, cough, night sweats, weight loss | Tropical disease            |                                                  | NR           | NR             | +         | +   |
| Neveling 1988 [28]    | Flue like symptoms, dry cough                           | Coccidiosis, histoplasmosis, North American blastomycosis |                                                  | NR           | NR             | NR        | +   |

Table A3. Signs and symptoms, differential diagnosis and diagnostic work-up.
| Study                      | Symptoms, Lesions, and Signs                                                                 | Diagnoses                                                                 | Biopsy Sites | Results |
|----------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|---------|
| Braeuninger et al. 1985    | Flue like symptoms, cervical lymphadenopathy, skin lesions, cough, dyspnea, pain in the left leg | Tuberculosis, sarcoidosis                                                 | Lymph node biopsy | ++      |
| Hastra et al. 1985         |                                                                                             |                                                                            |              |         |
| Altmeyer 1976 [31]         | Respiratory insufficiency, cervical lymphadenopathy, painful infiltrations of the soft palate, hypersalivation, ulcerations of the feet, weight loss, dysphagia, dysphonia | Tuberculosis, Wegner’s granulomatosis                                      | Lung and skin lesion biopsy | +       |
| Ferreira et al. 2017 [32]  | Labial lesion, dry cough, inguinal and axillary lymphadenopathy, weight loss                  | Cryptococcosis                                                           | Lip lesion and lung biopsy, inguinal lymph node resection | +       |
| Coelho et al. 2013 [33]    | Odynophagia, dysphagia, irregular and ulcerated oral mucosa                                 | NR                                                                        | Oropharyngeal mucosa biopsy | +       |
| Alves et al. 2013 [34]     | Skin lesion, oral mucosal ulcerations                                                        | Coccidioidomycosis, cutaneous tuberculosis                               | Skin lesion and oral mucosa biopsy | +       |
| Armas et al. 2012 [35]     | Ulcerated skin and nasal mucosa lesion                                                        | NR                                                                        | Skin lesion biopsy | +       |
| Carvalho et al. 2009 [36]  | Fever, epigastric pain, anorexia, fatigue, lymphadenopathy, skin lesions                     | NR                                                                        | Skin biopsy and lymph node | +       |
| Villar et al. 1963 [37]    | Full-text not available                                                                      |                                                                           |              |         |
| Oliveira et al. 1960 [38]  | Full-text not available                                                                      |                                                                           |              |         |
| SPAIN                      |                                                                                             |                                                                           |              |         |
| Chamorro-Tojeiro et al. 2020 [20] | Fever, arthralgia, myalgia, dyspnea, dry cough, sweating, general cutaneous rash                      | Bacterial respiratory infection                                           | NR           | NR      |
| Agirre et al. 2019 [19]    | Fever, productive cough, exertional dyspnea                                                  | Bacterial respiratory infection                                           | NR           | NR      |
| Molina-Morant et al. 2018 [18] |                                                                                             |                                                                           |              |         |
| Navascués et al. 2013 [39] | Productive cough, weight loss, asthenia, lymphadenopathy, skin lesions                      | NR                                                                        | Lung biopsy   | +       |
|                            |                                                                                             |                                                                           |              |         |
| Study                          | Symptoms                                                                 | Diagnosis            | Lesion biopsy       | Lung biopsy        | Skin biopsy | Oral mucosa biopsy |
|-------------------------------|---------------------------------------------------------------------------|----------------------|---------------------|-------------------|-------------|-------------------|
| Buitrago et al. 2011 [40]     | Fever, asthenia, ulcerated pustular skin lesions, extremities            | NR                   | Skin biopsy         | +                 | NR          | +                 |
|                               | Productive cough                                                         | NR                   | NR                  | +                 | NR          | +                 |
|                               | NR                                                                        | NR                   | Cerebral biopsy     | +                 | NR          | +                 |
|                               | NR                                                                        | NR                   | Lung biopsy         | NR                | +           | NR                |
|                               | NR                                                                        | Oral mucosa biopsy   | +                   | NR                | +           | +                 |
| Pujol-Riqué et al. 2011 [41]  | Productive cough, hemoptysis, night sweats, skin lesions                 | Sarcoidosis          | Lung and skin biopsy| −                 | +           | NR                |
| Ramírez-Olivencia et al. 2010 [42] | Fever, dyspnea, productive cough, hemoptysis, night sweats, loss of appetite, weight loss | | Lung biopsy | NR | − | + | + |
| Botas-Velasco et al. 2010 [43] | Cough, fever, weight loss, retromolar mass                              | Sarcoidosis          | Retromolar mass and laryngeal biopsy | + | + | + | NR |
| Mayayo et al. 2007 [44]       | Skin lesions                                                              | Blastomycosis        | Skin lesion biopsy  | +                 | NR          | NR                |
| López Castro et al. 2005 [45] | Dyspnea, dry cough, fever, weight loss, skin lesions                     | Sarcoidosis          | Lung and skin biopsy| +                 | NR          | −                 |
| Ginarte et al. 2003 [46]      | Ulcerative lesions from upper left jaw to labial mucosa and nasal grave | Squamous cell carcinoma | Lesion biopsy | + | + | + | NR |
|                               | Ulcerative lesions left cheek mucosa, periodontitis with loss of several teeth | Tuberculosis, squamous cell carcinoma | Lesion biopsy | + | + | NR | NR |
|                               | Mass and ulcerative lesions in cheek mucosa                              | Squamous cell carcinoma | Lesion biopsy | + | + | NR | NR |
| Garcia Bustínduy et al. 2000 [47] | Ulcerative skin lesion                                                   | NR                   | Skin lesion biopsy  | +                 | +           | +                 |
| Del Pozo et al. 1998 [48]     | Lesions upper labial mucosa and nasal fossa                              | NR                   | Lesion biopsy       | +                 | +           | NR                |
| Garcia et al. 1997 [49]       | Lesions of labial and palatal mucosa                                    | NR                   | Lesion biopsy       | +                 | +           | NR                |
| Source                                   | Clinical Manifestations                                                                 |
|-----------------------------------------|----------------------------------------------------------------------------------------|
| Pereiro et al. 1996 [50]                | Tumoral mass of the upper jaw, ulcerated lesion in the upper left jaw, extended to the | Epidermoid carcinoma | Lesion biopsy | + | + | + | NR |
|                                         | lip mucosa and the nasal grave                                                         |                          |              |   |   |   |    |
| Miguélez et al. 1995 [17]              | Fever, weight loss, dyspnea, ulcerated mass right tonsil, lymphadenopathy                | Pulmonary fibrosis       | Ulcerated mass biopsy | + | + | NR | NR |
|                                         | Palatal mass, cervical lymphadenopathy                                                 | NR                      | Palatal mass biopsy  | + | + | NR | NR |
| Pereiro Miguens et al. 1987 [16]        | Oral mucosal lesions, gingivitis                                                     | Tuberculosis            | Mucosa biopsy      | + | + | + | NR |
| Simon Merchán et al. 1970 [15]          | Full-text not available                                                               |                          |              |   |   |   |    |
| Pereiro Miguens et al. 1974 [14], Pereiro Miguens et al. 1972 [51] | Epididymitis, gingivitis, oral ulcerative lesion                                       | Tuberculosis            | Epididymis and oral lesion biopsy | + | + | + | NR |
|                                         | Asthenia, ulcerative oral lesions, labial edema                                        | NR                      | Oral lesion biopsy  | + | + | NR | NR |
| Vivancos et al. 1969 [13]               | Oral mucosal lesions                                                                  | Pseudoneoplasia         | Oral lesion biopsy | + | + | NR | NR |
| GREAT BRITAIN                           |                                                                                       |                          |              |   |   |   |    |
| De Cordova et al. 2012 [52]             | Submandibular mass, oral ulcerative lesions                                           | NR                      | Oral lesion and submandibular mass biopsy | + | + | NR | NR |
| Sierra et al. 2011 [53]                 | Dyspnea, lip lesion, ulcer on tonsil and uvula                                        | Malignancy, sarcoidosis, squamous cell carcinoma | Lip lesion excision, ulcer biopsy | + | NR | + | NR |
| Walker et al. 2008 [54]                 | Cough, dyspnea, plantar pruritus, painful skin lesions on his legs, face and feet, hepato megaly, weight loss | NR                      | Skin biopsy      | + | + | + | NR |
| Bowler et al. 1986 [55]                 | Cough, dyspnea, and wheeze on exertion                                                | Lymphangitis carcinomatosa | Lung biopsy | + | NR | + | NR |
| Symmers 1966 [56]                       | Asymptomatic                                                                          | Spleen (autopsy)        | + | NR | NR | NR |
| ITALY                                   | Skin ulceration                                                                       | Skin lesion excision    | + | NR | NR | NR |
| Reference          | Symptoms                                      | Diagnosis          | Procedure                      | +   | +   | NR  | NR  |
|--------------------|-----------------------------------------------|--------------------|--------------------------------|-----|-----|-----|-----|
| Borgia et al. 2000 | Fever, pain, and inflammation of left knee    | Malignancy         | Left femur biopsy              | +   | +   | NR  | NR  |
| Pecoraro et al. 1998 | Weight loss, night sweat, pain left knee     | NR                 | Left femur biopsy              | +   | NR  | NR  | NR  |
| Solaroli et al. 1998 | Skin lesion, asthenia, fever, loss of vision | NR                 | Skin lesion excision           | +   | +   | NR  | NR  |
| Fulciniti et al. 1996 | Weight loss, night, sweats, pain in left knee | Metastatic lung cancer | Left femur biopsy              | +   | +   | NR  | NR  |
| Cuomo et al. 1985  | Productive cough, weight loss, asthenia, skin lesions | Tuberculosis, lupus vulgaris | Lung and skin lesion biopsy    | +   | +   | +   | NR  |
| Benoldi et al. 1985 | Ulcerative skin lesions, cough, fatigue, malaise, weight loss | Tuberculosis, lupus vulgaris | Skin lesion biopsy              | +   | +   | +   | NR  |
| Finzi et al. 1980  | Full-text not available                       |                    |                                |     |     |     |     |
| Velluti et al. 1979 | Cough, dyspnea                                | Bronchitis, tuberculosi | Lung biopsy                   | +   | +   | +   | NR  |
| Lasagni et al. 1979 | Full-text not available                       |                    |                                |     |     |     |     |
| Scarpa et al. 1965 | Cough, asthenia, weight loss, night sweats, lymphadenitis, ulcerative oral lesions | Tuberculosis | Lymph node and lung biopsy     | +   | +   | NR  | NR  |
| Schiraldi et al. 1963 | Full-text not available                       |                    |                                |     |     |     |     |
| Molese et al. 1956 | Oral mucosa lesions, cervical lymphadenopathy, fever, cough | Tuberculosis, leishmaniosis, pneumoconiosis, lues, malignancy | Oral mucosa and tonsillar biopsy | +   | NR  | NR  | NR  |
| Farris 1955        | Full-text not available                       |                    |                                |     |     |     |     |
| Bertaccini 1934    | Full-text not available                       |                    |                                |     |     |     |     |
| Dalla Favera 1914  | Full-text not available                       |                    |                                |     |     |     |     |
| FRANCE             |                                               |                    |                                |     |     |     |     |
| Heleine et al. 2020 | Skin lesions, ulcero-nodular lesions lips and mouth, cough, fever, inguinal lymphadenopathy, asthenia, weight loss | HIV, tuberculosis | Skin biopsy                   | −   | +   | NR  | NR  |
| Dang et al. 2017   | Nodular slightly painful, nonulcerated lesion of the tongue, cervical lymphadenopathy | NR                 | Lingual lesion biopsy          | +   | NR  | NR  | +   |
| Authors               | Symptoms/Findings                                                                 | Diagnosis                                                                 | Biopsy/Excision Pathology | Paracoccidioides spp. | L. paracoccoides spp. | T. cruzi spp. | Fungal Structures | Microbiology | Signs and Symptoms |
|----------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------|-----------------------|----------------------|---------------|-------------------|--------------|-------------------|
| Sambourg et al. 2014 [74] | Partially ulcerous and crusted erythematous lesion left auricle extending to the pre-auricular region | Leishmaniosis                                                             | Skin lesion biopsy        | +                     | +                    | –            | +                | NR           |                   |
| Laccourreye et al. 2010 [75] | Dysphonia, laryngitis                                                            | Chronic laryngitis                                                        | Laryngeal biopsy, removed mucosa | +                     | +                    | NR           | NR               | NR           |                   |
| Poisson et al. 2007 [76] | Seizures                                                                         | Brain tumor                                                               | Single cerebral lesion surgically excised | +                     | +                    | +            | NR               | NR           |                   |

**NETHERLANDS**

| Authors               | Symptoms/Findings                                                                 | Diagnosis                                                                 | Biopsy/Excision Pathology | Paracoccidioides spp. | L. paracoccoides spp. | T. cruzi spp. | Fungal Structures | Microbiology | Signs and Symptoms |
|----------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------|-----------------------|----------------------|---------------|-------------------|--------------|-------------------|
| Van Damme et al. 2006 [77] | Dyspnea, cough, wheezing, weight loss, tiredness, fever, night sweats, periodontitis, oral ulceration | Sarcoidosis, bronchiolitis obliterans organizing pneumonia, oral carcinoma | Lung and oral mucosa biopsy | +                     | +                    | +            | NR               | NR           |                   |

**NORWAY**

| Authors               | Symptoms/Findings                                                                 | Diagnosis                                                                 | Biopsy/Excision Pathology | Paracoccidioides spp. | L. paracoccoides spp. | T. cruzi spp. | Fungal Structures | Microbiology | Signs and Symptoms |
|----------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------|-----------------------|----------------------|---------------|-------------------|--------------|-------------------|
| Maehlen et al. 2001 [78] | Dizziness, nausea, headache, hearing loss, hemiplegia                             | Cerebral tuberculosis                                                     | Brain biopsy              | +                     | +                    | NR            | NR               | NR           |                   |

**SWITZERLAND**

| Authors               | Symptoms/Findings                                                                 | Diagnosis                                                                 | Biopsy/Excision Pathology | Paracoccidioides spp. | L. paracoccoides spp. | T. cruzi spp. | Fungal Structures | Microbiology | Signs and Symptoms |
|----------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------|-----------------------|----------------------|---------------|-------------------|--------------|-------------------|
| Stanisic et al. 1979 [79], Wegmann et al. 1959 [80] | Submandibular and cervical lymphadenopathy, oral ulceration | Tuberculosis, Morbus Wegener, lues, bartonellosis, Morbus Hodgkin, neoplasma, blastomycosis, sporotrichosis, cryptococcosis | Oral mucosa and cervical lymph node biopsy | +                     | +                    | NR            | NR               | NR           |                   |

**Abbreviations:** NR, not reported or not performed; +, positive for *Paracoccidioides* spp.; –, negative for *Paracoccidioides* spp.; 1 Fungal structures were identified in at least one of the biopsy/excision specimen; 2 Microbiology includes microscopy and/or culture; 3 Signs and symptoms obtained for case 1 and case 2 obtained from Buitrago et al. 2009 [85].
References

1. Bocca, A.L.; Amaral, A.C.; Teixeira, M.M.; Sato, P.; Yasuda, S.M.A.; Felipe, S.M.S. Paracoccidioidomycosis: eco-epidemiology, taxonomy and clinical and therapeutic issues. *Future Microbiol.* 2013, 8, 1177–1191, doi:10.2217/fmb.13.68.

2. Hrycyk, M.F.; Garces, G.H.; Bosco, S.D.M.G.; de Oliveira, S.L.; Marques, S.A.; Bagagli, E. Ecology of Paracoccidioides brasiliensis, P. lutzii and related species: Infection in armadillos, soil occurrence and mycological aspects. *Med. Mycol.* 2018, 56, 950–962, doi:10.1093/mmy/mmy142.

3. Turissini, D.A.; Gomez, O.M.; Teixeira, M.M.; McEwen, J.G.; Matute, D.R. Species boundaries in the human pathogen Paracoccidioides. *Fungal Genet. Biol.* FG B 2017, 106, 9–25, doi:10.1016/j.fgb.2017.05.007.

4. Ameen, M.; Talhari, C.; Talhari, S. Advances in paracoccidioidomycosis. *Clin. Exp. Dermatol.* 2010, 35, 576–580.

5. Martínez, R. New trends in paracoccidioidomycosis epidemiology. *J. Fungi* 2017, 3, doi:10.3390/jf3010001.

6. Shankar, J.; Restrepo, A.; Clemons, K.V.; Stevens, D.A. Hormones and the Resistance of Women to Paracoccidioidomycosis. *Clin. Microbiol. Rev.* 2011, 24, 296, doi:10.1128/CMR.00062-10.

7. Brummer, E.; Castaneda, E.; Restrepo, A. Paracoccidioidomycosis: An update. *Clin. Microbiol. Rev.* 1993, 6, 89–117.

8. Wanke, B.; Aidé, M.A. Chapter 6-paracoccidioidomycosis. *J. Bras. Pneumol.* 2009, 35, 1245–1249.

9. Salzer, H.J.F.; Burchard, G.; Cornely, O.A.; Lange, C.; Rolling, T.; Schmiedel, S.; Libman, M.; Capone, D.; Le, T.; Dalcolmo, M.P.; et al. Diagnosis and Management of Systemic Endemic Mycoses Causing Pulmonary Disease. *Respiration* 2018, 96, 283–301, doi:10.1159/000489501.

10. Ajello, L.; Polonelli, L. Imported paracoccidioidomycosis: A public health problem in non-endemic areas. *Eur. J. Epidemiol.* 1985, 1, 160–165.

11. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PloS Med.* 2009, 6, 97, doi:10.1371/journal.pmed.1000977.

12. Innovation, V.H. Covidence Systematic Review Software. Available online: www.covidence.org (accessed on 2 June 2019).

13. Vivancos, G.; Marrero, B.; Hernández, B.; Padrón, G. La blastomicosis sudamericana en España. Primera observación en las Islas Canarias. In Proceedings of the VV. AA. Actas VII Congreso Hispano-Portugués de Dermatología Médico quirúrgica, Granada, Spain, 22–25 October 1969; pp. 330–335.

14. Pereiro, M.M. Two cases of South American blastomycosis observed in Spain. *Actas Dermosifiliogr.* 1974, 65, 509–522.

15. Merchán, S.A.; Escudero, R.; Lavin, R. Un caso de blastomicosis sudamericana observado en España. *Med. Cutan. Iber. Lat. Am.* 1970, 5, 631–636.

16. Miguens, P.M.; Ferreiros, P.M.M. A propósito de un nuevo caso de paracoccidioidomicosis observado en España. *Ver. Iber. Micol.* 1987, 4, 149–157.

17. Miguélez, M.; Amerigo, M.J.; Perera, A.; Rosquete, J. Imported paracoccidioidomycosis. Apropos of 2 cases. *Med. Clin. (Barc)* 1995, 105, 756.

18. Morant, M.D.; Montalvá, S.A.; Salvador, F.; Avilés, S.A.; Molina, I. Imported endemic mycoses in Spain: Evolution of hospitalized cases, clinical characteristics and correlation with migratory movements, 1997–2014. *PloS Negl. Trop. Dis.* 2018, 12, 6245, doi:10.1371/journal.pntd.0006245.

19. Agirre, E.; Osorio, A.; de Tejerina, C.F.J.M.; Arrondo, R.F.; Bermejo, S.Y. Bilateral interstitial pneumonia after recent trip to Peru. *Enferm. Infec. Microbiol.* Clin. 2019, 37, 609–610, doi:10.1016/j.eimc.2019.03.002.

20. Tojeiro, C.S.; Sarria, G.A.; Pedrosa, E.G.G.; Buitrago, M.J.; Vélez, L.R. Acute Pulmonary Paracoccidioidomycosis in a Traveler from Mexico. *J. Travel. Med.* 2020, 27, 10.1093/jtm/taaa018.

21. Wagner, G.; Moertl, D.; Eckhardt, A.; Sagel, U.; Wrba, F.; Dam, K.; Willinger, B. Chronic Paracoccidioidomycosis with adrenal involvement mimicking tuberculosis—A case report from Austria. *Med. Mycol. Case Rep.* 2016, 14, 12–16, doi:10.1016/j.mcmcr.2016.12.002.

22. Mayr, A.; Kirchmair, M.; Rainer, J.; Rossi, R.; Kreczy, A.; Tintelnot, K.; Dierich, M.P.; Flörl, L.C. Chronic paracoccidioidomycosis in a female patient in Austria. *Eur. J. Clin. Microbiol. Infect. Dis.* 2004, 23, 916–919.

23. Balabanov, K.; Balabanoff, V.A.; Angelov, N. South American Blastomycosis in a Bulgarian Laborer Returning after 30 Years in Brazil. *Mycopathol. Mycol. Appl.* 1964, 24, 265–270.

24. Kayser, M.; Rickerts, V.; Dric, N.; Gerkrath, J.; Kreipe, H.; Soudah, B.; Welte, T.; Suhling, H. Chronic progressive pulmonary paracoccidioidomycosis in a female immigrant from Venezuela. *Ther. Adv. Respir. Dis.* 2019, 13, 4913, doi:10.1177/1753466619894913.

25. Slevogt, H.; Tintelnot, K.; Seybold, J.; Sutter, N. Lymphadenopathy in a pregnant woman from Brazil. *Lancet* 2004, 363, 1282.

26. Horré, R.; Schumacher, G.; Alpers, K.; Seitz, H.M.; Adler, S.; Lemmer, K.; De Hoog, G.S.; Schaaf, K.P.; Tintelnot, K. A case of imported paracoccidioidomycosis in a German legionnaire. *Med. Mycol.* 2002, 40, 213–216.

27. Köhler, C.; Klotz, M.; Daus, H.; Schwarze, G.; Dette, S. Viseral paracoccidioidomycosis in a gold-digger from Brasil. *Mycoses* 1988, 31, 395–403.

28. Neveling, F. Paracoccidioidomycosis infections caused by an adventure vacation in the Amazon. *Prax. Klin. Pneumol.* 1988, 42, 722–725.

29. Brauninger, W.; Hastra, K.; Rubín, R. Paracoccidioidomycosis, an imported tropical disease. *Hautarzt* 1985, 36, 408–411.

30. Hastra, K.; Schulz, V.; Brauninger, A. South American blastomycosis in the Federal Republic of Germany. *Prax. Klin. Pneumol.* 1985, 39, 905.
62. Finzi, F.F.; Bubola, D.; Lasagni, A. Blastomycosi sudamericana. *Ann. Ital. Dermatol. Clin. Sper.* 1980, 34, 277–285.
63. Velluti, G.; Mazzoni, A.; Kaufman, L.; Covi, M. Physiopathological, clinical and therapeutical notes on a case of paracoccidioidomycosis. *Gazz. Med. Ital.* 1979, 138, 297–304.
64. Lasagni, A.; Innocenti, M. Su un caso di blastomycosi sud americana. *Chenioter. Antimicrob.* 1979, 2, 188–190.
65. Scarpa, C.; Nini, G.; Gualdi, G. Clinico-radiological contribution to the study of paracoccidioidomycosis. *Minerva Dermatol.* 1965, 40, 413–421.
66. Schiraldi, O.; Grimaldi, N. Granulomatosi paracoccidioido. *Policlinico* 1963, 70, 65–84.
67. Molese, A.; Pagano, A.; Pane, A.; Vingiani, A. Case of paracoccidioidal granulomatosis; Lutz-Splendore-Almeida disease. *Riforma Med.* 1956, 70, 1009–1014.
68. Farris, G. Report on a case of paracoccidioidomycosis (so-called Brazilian blastomycosis). Atti della Società italiana di dermatologia e sifilografia e delle sezioni interprovinciali. *Soc. Ital. Dermatol. Sifilogr.* 1955, 96, 321–358.
69. Bertaccini, G. Contributo allo studio della cosi detta≪ blastomicosi sud-americana >>. *Giorn. Ital. Dermatol. Sifil.* 1934, 75, 783–828.
70. Dalla Faveria, G.B. Per la conoscenza della cosidetta blastomycosi cutanea (con un’osservazione personale di oidiomicosi (Gilchrist, Bushke) zimonematosi (de Beurmann et Gougerot). Giorn. Ital. Mal. Ven. Pelle (Gilchrist, Bushke) zimonematosis (de Beurmann et Gougerot). Giorn. Ital. Mal. Ven. Pelle 1914, 55, 650–729.
71. Heleine, M.; Blaizot, R.; Cissé, H.; Labaudi nière, A.; Guerin, M.; Demar, M.; Blanchet, D.; Couppee, P. A case of disseminated paracoccidioidomycosis associated with cutaneous lobomycosis. *J. Eur. Acad. Dermatol. Venereol.* 2020, 34, e18–e20, doi:10.1111/edv.15863.
72. Dang, J.; Chanson, N.; Charlier, C.; Bonnal, C.; Jouvon, G.; Goulenok, T.; Papo, T.; Sacre, K. A 54-Year-Old Man with Lingual Granuloma and Multiple Pulmonary Excavated Nodules. *Chest* 2017, 151, e13–e16, doi:10.1016/j.chest.2016.07.026.
73. Sambourg, E.; Demar, M.; Simon, S.; Blanchet, D.; Dufour, J.; Marie, S.D.; Fior, A.; Carne, B.; Aznar, C.; Couppee, P. Paracoccidioidomycosis of the external ear. *Ann. Dermatol. Venereol.* 2014, 141, 514–517, doi:10.1016/j.annder.2014.04.121.
74. Laccourreye, O.; Mirghani, H.; Brasnu, D.; Badoul, C. Imported acute and isolated glottic paracoccidioidomycosis. *Ann. Otol. Rhinol. Laryngol.* 2010, 119, 89–92.
75. Poisson, D.M.; Heitzmann, A.; Mille, C.; Muckensturm, B.; Dromer, F.; Dupont, B.; Hochqueloux, L. Paracoccidioides brasiliensis in a brain abscess: First French case. *J. Mycol. Med.* 2007, 17, 114–118.
76. Van Damme, P.A.; Bierenbroodspot, F.; Telgt, D.S.C.; Kwakman, J.M.; De Wilde, P.C.M.; Meis, J.F.G.M. A case of imported paracoccidioidomycosis: An awkward infection in the Netherlands. *Med. Mycol.* 2006, 44, 13–18.
77. Maehlen, J.; Strøm, E.H.; Gerlyng, P.; Heger, B.H.; Orderud, W.J.; Syversen, G.; Solgaard, T. South American blastomycosis--a differential diagnosis to tuberculous meningitis. *Tidskr. Nor. Laegeforening* 2001, 121, 33–34.
78. Stanisic, M.; Wegmann, T.; Kuhn, E. South American blastomycosis (paracoccidioidomycosis) in Switzerland. Clinical course and morphological findings in a case following long-term therapy. *Schweiz. Med. Wochenschr.* 1979, 109, 693–699.
79. Wegmann, T.; Zollinger, H.U. Tuberkuloide Granulome in Mundscheinhaut und Halslymphknoten: Sudamerikanische Blastomykose. *Schweiz. Med. Wochenschr.* 1959, 89, 2–8.
80. Bonifaz, A.; González, V.D.; Ortiz, P.A.M. Endemic systemic mycoses: Coccidioidomycosis, histoplasmosis, paracoccidioidomycosis and blastomycosis. *J. Ger. Soc. Dermatol.* 2011, 75, 705–716.
81. Buitrago, M.J.; Estrella, C.M. Current epidemiology and laboratory diagnosis of endemic mycoses in Spain. *Enferm. Infecc. Microbiol. Clin.* 2012, 30, 407–413.
82. Júnior, Q.R.; Tde, G.A.; Massucio, R.A.; De Capitani, E.M.; Sde, R.M.; Balthazar, A.B. Association between paracoccidioidomycosis and tuberculosis: Reality and misdiagnosis. *J. Bras. Pneumol. Publicacao Soc. Bras. Pneumol. Tisiologia* 2007, 33, 295–300, doi:10.1590/s1806-37132007000300011.
83. Telles, Q.F.V.; Petrobom, P.P.M.; Júnior, R.M.; Baptista, R.M.; Peçanha, P.M. New Insights on Pulmonary Paracoccidioidomycosis. *Semin. Respir. Crit. Care Med.* 2020, 41, 53–68, doi:10.1055/s-0039-3400544.
84. Pecoraro, C.; Pinto, A.; Tortora, G.; Ginolfi, F. South American blastomycosis of the lung and bone: A case report. *Radiol. Med.* 1998, 95, 521–523.
85. Buitrago, M.J.; Merino, P.; Puente, S.; Lopez, G.A.; Arribi, A.; Oliveira, Z.R.M.; Gutierrez, M.C.; Tudela, R.J.L.; Estrella, C.M. Utility of Real-time PCR for the detection of Paracoccidioides brasiliensis DNA in the diagnosis of imported paracoccidioidomycosis. *Med. Mycol.* 2009, 47, 879–882.