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REVIEW ARTICLE

Pathogenesis and Classification of Paracocidioidomycosis: New Insights From Old Good Stuff

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Different classifications of paracoccidioidomycosis emerged since its discovery in 1908, culminating in the proposition of a simplified and consensual one in 1987. However, by revisiting these classifications, case reports, or case series from which the authors based their own, we found many patients who did not fit in either the 1987 classification or in the correspondent natural history/pathogenesis view. In this report, the concepts of paracoccidioidomycosis infection, primary pulmonary paracoccidioidomycosis (PP-PCM), and other subclinical forms of PCM are reassessed. A classification is proposed to encompass all these subtle but distinct outcomes. I suggest a continuum between the PP-PCM and the overt chronic form of disease, and not the current view of quiescent foci, frozen in time and suddenly reactivated for unknown reasons. Failure to fully resolve the infection in its initial stages is a conceivable hypothesis for the chronic form. The proposed clinical classification might offer new insights to better characterize and manage PCM patients.

Keywords. classification; immune response; paracocidioidomycosis; pathogenesis; subclinical infection.

Paracoccidioidomycosis (PCM) is a systemic mycosis caused by fungi of the genera *Paracoccidioides*, *Paracoccidioides brasiliensis*, and *Paracoccidioides lutzii*. Both cause progressive clinical forms that can be acute or subacute, rare, or chronic, corresponding to ≥90% of the patients. The infection is acquired through inhalation of mycelial propagules, and it is the most important endemic fungal infection in Latin America. Paracoccidioidomycosis is a polymorphic disorder that may affect any system and organ. The disease was first described in 2 patients in 1908 by Adolfo Lutz in São Paulo, Brazil. Since then, several different classifications of the mycosis have emerged; the initial classifications date back to the 1940s and were mainly based on the topography of lesions. Subsequent classifications evolved to include aspects of pathogenesis and natural history of the disease as understood at the time, better characterization of the polymorphic clinical manifestations, and eventually the patients' immunoreactivity status. The most recognized classifications are shown in Supplementary Figures 1 and 2. The variability in clinical classifications prompted a committee of South American experts to propose a unified classification (Table 1), based on the pathogenesis and natural history of the disease, which was published in 1987 [1].

Parallel to this, the immune response associated with the disease started to be investigated. Some authors proposed schemes to summarize the major findings, and they tried to fit them in the 1987 simplified classification of the disease [2–5]. However, by revisiting the successive classifications of the disease over time (with respective views on its natural history and pathogenesis) and case reports or case series from which the authors based their classification, we found that many patients did not in fit either the 1987 classification or in its correspondent natural history or pathogenesis view, nor in the proposed immunological schemes.

Although the present analysis revisits old findings, it may have direct implications in the current management of the mycosis. This can be illustrated by the present dilemma in coccidioidomycosis, regarding the benefits of administering antifungal therapy to uncomplicated primary pulmonary coccidioidomycosis [6]. Reports suggest that early treatment alters immunologic responses and favors late emergence of disseminated infection [7, 8]. This dilemma would only be solved by a better understanding of the pathogenesis of early coccidioidomycosis manifestations. In PCM, this dilemma has already been discussed by several authors 40 to 60 years ago when diagnosing asymptomatic subjects with "subclinical," "regressive" or "PCM-infection" [9–12]. Nonetheless, this issue in PCM still remains unsolved.

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Table 1. 1987 Classification of Paracocciodioidomycosis

1. Paracocciodioidomycosis Infection
2. Paracocciodioidomycosis Disease
Acute or Subacute Form (Juvenile Type)
• Moderate
• Severe
Chronic Form (Adult Type)
• Unifocal
• Mild
• Moderate
• Severe
• Multifocal
• Mild
• Moderate
• Severe
3. Residual Forms (Sequelae)

Reproduced from [1].

CLASSIFICATION GAPS

This review revisits previous classifications of PCM that culminated in the current simplified classification. The discussion is divided in 2 main topics below: Paracoccidioidomycosis-Infection and Primary Pulmonary Paracoccidioidomycosis.

PARACOCCIDIOIDOMYCOSIS INFECTION?

As in other systemic mycoses, a large proportion of individuals in endemic areas who have been infected will never develop clinical signs of the mycosis. This was established in 1959 by Lacaz et al [9] who described asymptomatic subjects with a positive *Paracoccidioides* antigen skin test, some of whom concurrently presented with chest x-ray abnormalities and/or positive titers on serological assays, indicating active PCM disease. The interpretation of the clinical meaning of these findings remained elusive [9]. There was no indication of how this small subgroup should be classified other than the positive skin test with normal chest x-ray and negative serology group. However, perhaps inadvertently, they were referred to as either as "patients" or "subjects." Close follow-up and eventually initiation of antifungal therapy of these patients, based on the "size and radiologic characteristics", were suggested. In 1964, another survey showed similar results: 13.0% of those with a positive skin test had positive serological tests. In addition, 19 of the 40 individuals with positive skin tests and who underwent chest x-ray evaluation showed nonspecific pulmonary abnormalities, including increased bronchial vascular network, diffuse shadowing of lower regions, micronodules, nodules with higher radiological density, and opacifications on lower zones [10]. Indeed, these abnormalities are usually seen in patients with the pulmonary chronic form (CF) PCM. However, attempts to identify *Paracoccidioides* forms in sputum samples of these individuals failed. It was suggested that such cases corresponded to "subclinical" PCM and, based on the previous findings of Lacaz et al [9], should be monitored and eventually treated. Thus, it appears that there are some individuals with subclinical disease among the infected but asymptomatic individuals in endemic areas, thus distinct from the infected asymptomatic group but still classified as PCM infection; those individuals could eventually benefit from antifungal therapy. Unfortunately, there is no mention of follow-up of these cases.

Several skin test surveys in endemic areas have been published since these initial studies, but researchers did not systematically search for subclinical cases, except when ruling out the presence of clinical signs of active disease (see 13–15). The existence of a subclinical form, as opposed to the truly uneventful PCM infection, has been supported in many studies thereafter (see 16); however, it was not included in the 1987's classification. An illustrative case reported a woman living in an endemic area with repeatedly positive results on a serological test and without any clinical or radiologic evidence of the disease. It is interesting to note that serum reactivity decreased gradually during the 2-year follow-up [17].

The issue of the PCM infection category comprising a heterogenous group of individuals is reinforced when examining the many PCM case reports and case series papers dating back to the 1970s (see 18–24). Such reports describe patients classified as asymptomatic PCM as a result of the mycosis being diagnosed by chance or in autopsies. In general, those patients presented heterogeneous clinical and radiologic features, which were reflected on the classifications they received: benign form, regressive form or regressive primary pulmonary form, paracoccidioidoma, primary pulmonary lymph node complex, or just asymptomatic form. The diagnosis resulted from the identification of some typical multibudding *Paracoccidioides* yeast cell among many nontypical or single-budding yeast cells. These cases created confusion about what is considered asymptomatic PCM, once the infectious process did not translate into discernible symptoms, but there was detectable tissue damage that led to the diagnosis of the mycosis.

The heterogeneous classification of some asymptomatic cases illustrates the different ways these patients were identified, classified, or managed (Table 2). Based on the case reports and accompanying classifications, it is not clear which cases should be considered a PCM infection or a disease with a benign presentation (or the equivalent names henceforth), or which of these patients should require close follow-up and/or treatment.

Finally, 2 definitions are commonly used to differentiate PCM infection from PCM disease, but both reveal shortcomings. First, it is assumed that individuals with PCM infection would present unapparent residual lesions (foci) containing viable but quiescent or dormant yeast cells. However, as it emerges from the old good data above, all of the reported asymptomatic individuals or patients had variable proportions of actively replicating yeast cells within the residual foci, mainly single-budding, but rarely multibudding. Thus, these lesions

Table 2. Illustrative Asymptomatic PCM Cases: Clinical, Mycological, and Histopathological Features, Classification, and Management

Age/Sex [ref]	59 y–o/M [20]	61 y–o/M [21]	42 y–o/F [24]	Adult/M [18]
Clinical Features	Pneumectomy for a poorly differentiated carcinoma	Death from intraoperative complications of a gastroenteroanastomosis.	Accidental fiding of a cavitary lesion on upper right lobe during a routine check-up, which remained unchanged and without diagnosis for 6 months	Asymptomatic infiltrative lesions on middle lower lung fields for 7 years with ongoing calcification
Histopathology	Excised lung: granulomatous inflammation amidst neoplasm tissue bundles and in 2 mediatinal and hilar nodes	Autopsy: pleural adhesions and ten 0.3- to 0.6-cm nodules in the apex of right lung: 9 with caseosis necrosis circumscribed by fibrosis; 1 fibrotic nodule	Open lung biopsy: granulomatous reaction with central caseosis necrosis	Open lung biopsy: encapsulated nodule with caseosis necrosiss
Mycology	Few yeast cells inside Langhans and foreign body giant cells, some single-budding, rare multibudding; a node with caseosis necrosis and many yeast cells some single-budding few mulltibudding	Many fungi within the caseosis necrosis some single-budding, rare multibudding	Many yeast cells, some single-budding, rare multibudding	Moderate number of yeast cells, a few multibudding
Diagnosis	Primary pulmonary lymph node complex PCM	Spontaneously healed pulmonary paracoccidioidal lesions	Asymptomatic chronic pulmonary PCM	Subclinical or benign form of PCM disease
Antigunfal Therapy/ Follow-up	No/NI	No/NI	Itraconazole/resolution	No/numerous calcified nodules after 12 years of follow-up

Abbreviations: F, female; M, male; NI, not informed; PCM, paracoccidioidomycosis; ref, ; y–o, year-old.

not only have the potential for future endogenous "reactivation," as stressed by Restrepo [25], but also hurt the paradigm of Th1-driven immune responses that fully control the infection, that is, fungus multiplication and spread [26], admitted for those individuals with PCM infection. The second definition is the asymptomatic presentation of the infectious process that characterizes the PCM infection. However, PCM disease is well known for its clinical-radiological dissociation. Patients with overt pulmonary involvement of the CF diagnosed by chest imaging may present without any accompanying symptom, whether respiratory or systemic [27]. There are reports on asymptomatic patients with isolated but gross adrenal lesions, which were diagnosed by chance [18]. Therefore, lack of signs or symptoms can also be misleading.

PRIMARY PULMONARY PARACOCCIDIOIDOMYCOSIS?

In 1965, Negroni and Negroni proposed, for the first time, a classification of the mycosis with a symptomatic primary pulmonary paracoccidioidomycosis (PP-PCM) form separated from the asymptomatic PCM infection [28], which was either omitted or reincluded in the many subsequent classifications [29–35]. This "comes and goes" practice helps to explain the difficulties in devising a classification of the initial, subclinical forms of PCM, which were, in fact, absent from the 1987's classification. In 2004, we reported an acute/subacute form (A/SAF) patient with clinical and radiologic findings of the symptomatic PP-PCM [36]. It is interesting to note that, although the primary pulmonary infiltrate resolved spontaneously without leaving residual fibrosis (contrary to the patients with the pulmonary CF), the infection disseminated to a generalized involvement of deep and superficial lymph nodes and marked hepatosplenomegaly. Based on this case, we hypothesized that A/SAF patients lack pulmonary residual fibrosis due to their profoundly depressed anti-*Paracoccidioides* immune response, resulting in loose granuloma [37], which would not mature and evolve to dense fibrosis. Following the literature, we have identified only 5 additional reports of patients with presumed diagnosis of an ongoing PP. In all except 1 patient, the specific diagnosis was delayed, allowing spontaneous resolution of the clinical-radiological findings of the PP-PCM, while the disseminated extrapulmonary disease persisted [12, 38–41]. Thus, the symptomatic PP-PCM presentation can occur in patients developing the A/SAF, a form of the disease believed to spare the lungs according to the 1987's classification [1]. That there are very few reports of such forms may be due to lack of symptoms at this early stage, or to absence of residual lesions at later stages. The underreporting of A/SAF patients with PP-PCM would mistakenly suggest that it constitutes a rare presentation of the disease. Londero et al [34] have previously proposed the existence of a progressive primary pulmonary form based on the observation of an A/SAF patient with isolated progressive pulmonary disease arising directly from PP-PCM. It is remarkable that this rarely described form is by far the most common presentation of the PCM's kindred systemic mycoses (coccidioiodomycosis, blastomycosis, and histoplasmosis).

Lung involvement in the A/SAF is still controversial. Londero et al's [34] group claimed that respiratory involvement in A/SAF children was more common than usually recognized, although most of the cited cases presented mediastinal and hilar lymph

node enlargement but no parenchymal abnormalities on the chest x-ray [35]. However, Restrepo et al [42] described A/SAF patients who did not present with respiratory symptoms or chest x-ray abnormalities and in whom *Paracoccidioides* sp was identified in induced sputum samples, pointing to the colonization of lungs with the fungus even in the A/SAF. An autopsy study of 13 A/SAF patients showed a few macroscopic alterations in the lungs, whereas microscopic alterations were present in all cases, characterized by small loose granulomas with few fungi in the alveolar septa with miliary distribution, macrophagic alveolitis, and interstitial pneumonitis [43]. The observation of respiratory symptoms (eg, cough and expectoration) in patients with no pulmonary abnormalities detected in the x-ray is consistent with these findings [34, 44]. Such findings may not be related to the initial primary pulmonary foci, but they would represent late pulmonary invasion through lymphohematogenous route by fungi released from the generalized lymph node involvement typical of A/SAF. One possibility to reconcile the mycological and pathological observations with the lack of pulmonary imaging abnormalities is that the small and loose inflammatory foci in the pulmonary parenchyma had size and density below the detection limit of routine chest x-ray exams, eg, less than 5 mm. Systematic high-resolution computed tomography investigation would shed light on the timing and type of pulmonary involvement in such cases.

A NEW CLASSIFICATION: "FILLING THE GAPS"

A classification is proposed to encompass all of these subtle but distinct outcomes. Finally, the issue of immunological correlates is discussed.

Individuals living in endemic areas are infected through inhalation of *Paracoccidioides* conidia, most frequently at young ages, according to epidemiological surveys. Once the conidia (3–5 μm in size) reach the terminal airways, temperature-driven transformation into the yeast form ensues. The role of inoculum size or frequency of re-exposure awaits further investigation. Both the way yeast cells invade human epithelial cells and the initial steps of the innate immune response are still an area of intense research [45]. As in other systemic mycoses, and similar to tuberculosis, there is an initial unrestricted pathogen multiplication that establishes a pulmonary parenchyma focus with involvement of hilar draining lymph nodes, the PP-PCM. Adaptative immune responses occur after 2–3 weeks and halts this process through a granulomatous inflammatory response. This process generally progresses without any clinical manifestation or may eventually manifest as a flu-like syndrome. Rarely, such a process is associated with mild pulmonary infiltrates and enlarged hilar/mediastinal nodes on chest X-ray, when it is misdiagnosed as bacterial pneumonia. Most often, this process evolves to clearance of the fungus with healing of the initial focus, leaving neither viable yeast cells nor significant tissue damage (the healed form). This protective immune response results in a positive paracoccidioidin skin test, which can wane over the long term if the individual leaves the endemic area and averts antigen re-exposure.

There are 4 additional outcomes of the PP-PCM other than sterile clearance that are far less frequent but clinically more relevant, namely, persistent infection, subclinical PCM form, PP-PCM form, and A/SAF. In a small number of the individuals, the PP-PCM involutes and leaves viable quiescent yeast cells within residual fibrotic foci, which characterizes the persistent infection form. These stable quiescent foci would remain well circumscribed throughout life, carrying an environment that limits active fungi replication. Over time, these fungi lose their viability, but the foci may retain fungal antigens. These stable foci do not usually evolve into disease unless there is severe immunosuppression while the fungi are still viable. Possible causes of severe systemic immunosuppression are acquired immune deficiency syndrome, cancer, and transplantation. Otherwise, these individuals are also paracoccidiodin skin test positive, and together with the healed form constitute the Th1-driven immune response pole of PCM. In a subgroup of individuals, the PP-PCM also involutes, but, differently from the PCM infection form, there is asymptomatic and usually mild tissue damage provoked by a persistent granulomatous inflammation. The lesions present with caseosis necrosis and viable fungi, some single budding, few multibudding (subclinical PCM form). The fact that the microenvironment within these subclinical lesions allows fungi to thrive (ie, supplying carbon and hydrogen sources, microaerophilia, and other unknown factors) suggests that they are less stable, and that the subtle host-parasite balance can be disturbed by endogenous and exogenous factors, resulting in the gradual progression (years or decades) to the CF disease. Common exogenous factors likely are smoking habit (present in >90% of the CF patients) and chronic alcohol abuse (~50% of the CF patients), which, albeit not strictly immunosuppressive, can lead to immune alterations that gradually disturb the local host-parasite balance. This subgroup stays intermediary to the resolution and progression arms of the host-parasite interplay. The CF disease would be the late result of the subclinical PCM outcome.

Very rarely, the PP-PCM follows unchecked: epidemiological surveys indicate that the humans are innately resistant to the fungus. In these rare cases, the PP-PCM stage tends to pass unnoticed for a different reason than that of the involution arm discussed above. The anti-*Paracoccidioides* immune response in these individuals is insufficient to elicit an inflammatory response that would result in clinical-radiological abnormalities. Alternatively, when lung lesions are present, they tend to subside spontaneously while the fungus spread through the lymphatic system to cause the typical overwhelming A/SAF of the disease. In these cases, the lungs can be recolonized by the fungus via hematogenous route, as several observations suggest.

A few case reports indicate that some A/SAF patients, mainly children, can suffer a progressive primary pulmonary form after the unchecked PP-PCM, where the pulmonary manifestations are prominent compared with the systemic lymphatic manifestations (the PP-PCM form). In these cases, the pulmonary involvement predominantly consists of consolidations and pleural thickening/effusion, lacking the fibrotic component commonly seen in the CF [34]. There are some attempts to subgroup the A/SAF into varieties according to the predominant organ involvement aimed at facilitating clinical suspicion and scoring the severity of this form of the disease [31, 32, 46].

The subsequent events in the natural history of PCM are less disputed and are shown in the scheme 1n Figure 1. However, one relevant point must be noted. We know that the sixth clinical form, CF, evolves conspicuously, with the initial focus being occasionally demonstrated many years before searching medical assistance [22]. This is also true for pulmonary and extrapulmonary foci. The CF patients are generally diagnosed while already presenting sizable amounts of mature fibrotic lesions adjacent to active, yeast-containing lesions. This suggests a continuum between the PP-PCM and the overt CF disease and not the current view of quiescent foci that stay frozen in time (years or decades) due to the host's effective Th1-driven immune response, and which suddenly reactivates for unknown reasons. Some degree of failure to fully resolve the infection since its initial stages is a conceivable hypothesis for these patients. Supplementary Figure 3 shows a schematic view of the proposed pathogen-associated immune pathways that result from the 3 principal outcomes of the infection: resolution, progression, and intermediary. Finally, Table 3 shows the proposal of a comprehensive clinical classification, which summarizes the scheme depicted in Figure 1.

CONCLUDING REMARKS

Systemic endemic mycoses such as coccidioidomycosis, histoplasmosis, and blastomycosis reveal our incomplete understanding of the complex fungus-host interplay. Paracoccidioidomycosis, in turn, seems to display an even more complex interplay: differently from the other systemic mycoses, its main clinical outcome, the CF (corresponding to >90% of the patients), does not evolve directly from the PP-PCM but from subclinical foci containing fungi that remained active or latent for, not infrequently, several decades, thus resembling more tuberculosis with its latency.

However, current immunological schemes barely account for clinical stages such as latent disease, with its instable or dynamic nature, or for the highly diverse and subtle clinical

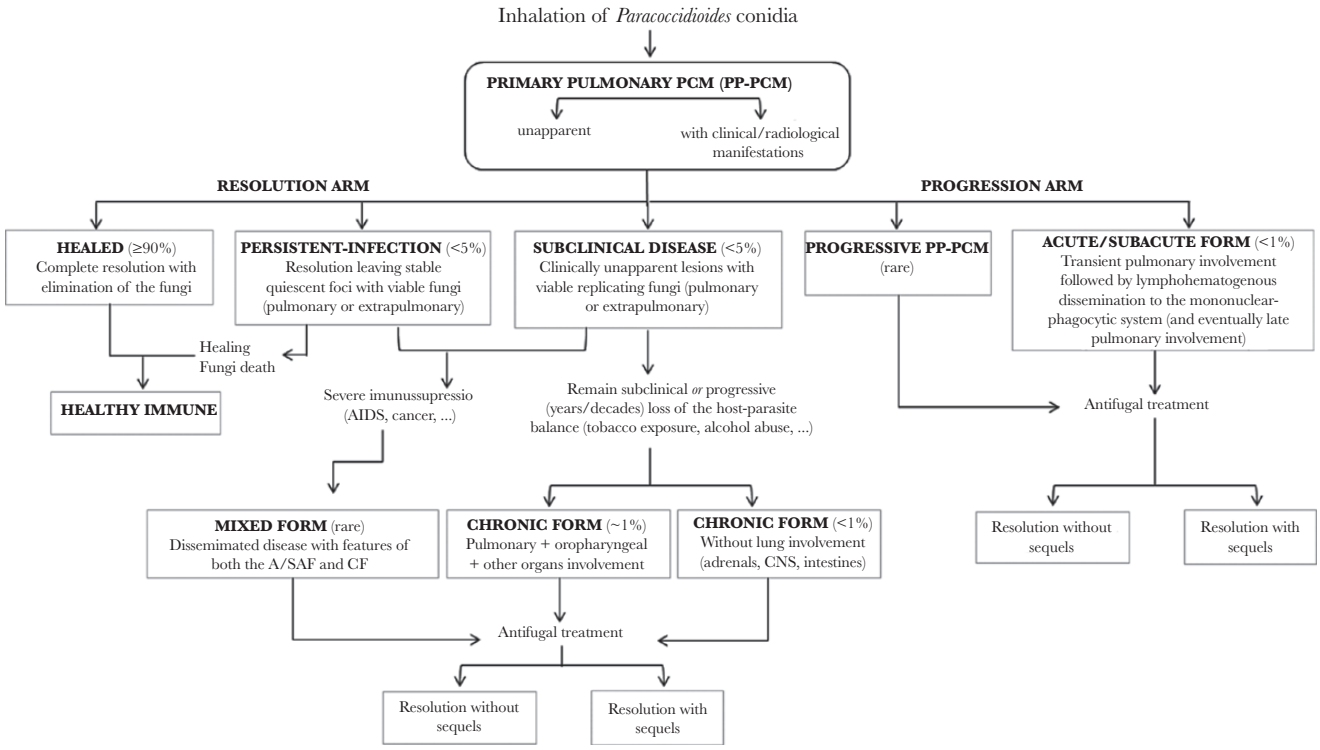

Figure 1. Schematic view of the natural history/pathogenesis of the *Paracoccidioides*-host interaction, highlighting the main clinical outcomes (in bold). The number in parenthesis indicates an estimated frequency of the outcome from the total of individuals infected in endemic areas. Individuals infected in endemic areas usually represent 10% to 60% of the local population. A/SAF, acute/subacute form; AIDS, acquired immune deficiency syndrome; CF, chronic form; CNS, central nervous system; PP-PCM, primary pulmonary paracoccidioidomycosis;

Table 3. Proposed Paracoccidioidomycosis Classification

Assymptomatic infection[a]	• Healthy imune[b] • Persistent infection[b] • Subclinical disease[b]	-
Primary progressive disease	• Acute/subacute form	• Lymphatic involvement • Bony • Pulmonary
Postprimary disease	• Chronic form	• Pulmonary • Extrapulmonary • Disseminated
	• Mixed form	• Immunosuppressed patients
Posttreatment	• Full recovery	
	• Sequels	• Pulmonary fibrosis • Adrenal insufficiency • Laryngeal stenosis • Dysphonia • Microstomia, etc

[a]The primary pulmonary infection may eventually cause mild, self-limited symptoms.

[b]These forms await better clinical, mycological, and immunological characterization of concepts such as latency, persistent infection, subclinical disease, regressive form, etc. These conditions blunt the conventional distinction between infection vs disease, as discussed in Casadevall A and Pirofski LA. The damage-response framework of microbial pathogenesis. Nat Rev Microbiol. 2003;1:17–24 and Lin PL and JL Flynn. The End of the Binary Era: Revisiting the Spectrum of Tuberculosis. J Immunol. 2018;201:2541–2548.

outcomes usually described in the clinical practice, such as those seen in systemic mycoses. Instead, immunological studies have traditionally addressed the host-parasite interaction through a susceptibility versus resistance angle. Immunological studies most often try to decipher the mechanisms that take place in patients that would result in either circumscribing or killing the invading yeast cells, thereby impeding their spread or toxic effects (resistant phenotype), or in failure to do so (susceptible phenotype). The natural history of these chronic infectious diseases does not truly fit into this dichotomous view, and thus lack a knowledgeable immunological background. The intermediary forms would perhaps be better described immunologically as a type of persistent or pathogen-induced tolerant state. Tolerance is characterized by events in which the host's immune network regulates inflammatory responses to avoid tissue damage rather than eliminate the agent that triggered the immunological insult. In infectious diseases, these mechanisms are not known: for example, the immune network that allows the life-time persistence of *Helicobacter pylori* within the gastric mucosa [47], or the one that allows persistence of *Mycobacterium tuberculosis*-viable bacilli within Gohn's complex and, as a result, better modeling assumptions to evaluate progression from latent infection to active disease [48]. In PCM, the question remains as to why some individuals who, albeit mounting Th1-driven granulomatous inflammation that circumscribes the yeast cells, still do not clear the infection, allowing persistence through continuous (low) level replication in subclinical foci. This missing knowledge also helps to explain the difficulties in defining what is success in treating primary uncomplicated coccidioidomycosis [6].

An alternative comprehensive approach has been recently proposed by Casadevall and Pirosfki [49] and termed response-damage framework, which may offer clues to better understand complex host-parasite interactions such as those underlying systemic mycoses. The framework is based on 3 tenets: (1) microbial pathogenesis is an outcome of the interaction between the host and microorganism: (2) the host outcome of the host-microorganism interaction is determined by the amount of damage to the host; and (3) host damage can result from microbial factors and/or host response. However, the damage-response framework still has some open issues such as the requirement of better quantitative and qualitative measures of the immune response and host damage, which is not provided by the current immunology research paradigm, as well as definition of the threshold that distinguishes host damage from clinical disease. These gaps certainly apply and help to explain our difficulties in devising a classification system for PCM.

In conclusion, we have proposed a clinical classification of PCM that incorporates observations from old but good data, which might offer new insights or clues to better classify and manage patients with this mycosis, and also provoke those in basic or applied research to elucidate the distinct mechanisms that underly the heterogenous outcomes of the host-parasite interaction and evolution.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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