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section 8 Infectious diseases 1364 Central nervous system involvement Coccidioidal meningitis may be accompanied by coccidioma, vas- culitis, infarction, and hydrocephalus. Most clinicians initiate treat- ment of meningitis with high-dose fluconazole (800–2000 mg/day), which can be reduced as the patient improves. Lifelong treatment is necessary. Obstructive hydrocephalus requires ventriculoperitoneal shunting. Selection of antifungal agents Antifungal therapy of primary coccidioidomycosis remains contro- versial, with no randomized trials comparing different treatments. One observational study indicated that clinicians were more likely to treat patients with more severe disease or culture positivity. Disseminated disease developed in 10% of the treated patients, indicating that treatment of primary disease does not guarantee a benign future course. Azoles are preferred for treating most forms of coccidioidomycosis. Fluconazole and itraconazole appear simi- larly effective, but fluconazole is usually chosen because of fewer adverse reactions. For either drug, 400 mg/day is usually given for a year or more after clinical cure. In HIV-infected patients with nonmeningeal disease, antifungal therapy may be stopped if their fungal disease is quiescent and their CD4 count has increased above 250 cells/μl with antiretroviral therapy. In meningitis, fluconazole has replaced intrathecal amphotericin B. Intrathecal amphotericin B is difficult to administer, and can cause arachnoiditis and vasculitis. A case-controlled study of coccidioidal meningitis comparing treat- ment with amphotericin B (primarily intrathecal) to fluconazole indicated that the neurologic complication rate (strokes, hydroceph- alus, and so on) and the overall mortality (39–40%) were similar in both groups, with survivors commonly having persistent neuro- logical deficits. Thus, fluconazole therapy for coccidioidal menin- gitis, although better tolerated and easier to administer, has not been

associated with an improved prognosis. Posaconazole has also been used for primary therapy in a series of 20 patients with chronic pulmonary or nonmeningeal dissemin- ated disease. Of these 20 patients treated for up to 6 months, 17 had a satisfactory clinical response. Posaconazole is licensed in Europe for salvage therapy of coccidioidomycosis, based on limited clin- ical experience. Posaconazole may succeed in cases of dissemin- ated nonmeningeal coccidioidomycosis in which other azoles and amphotericin B have failed. The dose is 200 mg four times daily, given orally with a high-fat meal. Voriconazole has been used successfully in cases of refractory coccidioidomycosis, including meningitis, and there are now some data showing efficacy of isavuconazole. Amphotericin B should be used largely as salvage therapy and in pregnancy, since azoles are teratogenic. If amphotericin B is toxic or not successful, in the last two trimesters of pregnancy fluconazole may be used with less risk of teratogenicity. After therapy has been stopped, the patient should be observed for years as coccidioido- mycosis has an unpleasant propensity to relapse. In vitro testing of antifungals in coccidioidomycosis typically shows susceptibility, and such testing is not helpful. The echinocandins have not been shown to be of value for the treatment of coccidioidomycosis. Recently, antifungal prophylaxis has been recommended for trans- plant recipients living in highly endemic areas. Nevertheless, the mor- tality rate remains high (29%) for transplant recipients who develop coccidioidomycosis while receiving prophylaxis. Patients with a his- tory of coccidioidomycosis may receive solid organ transplants when the disease is inactive and if they maintain lifelong azole therapy (e.g. fluconazole 400 mg/day). Antifungal prophylaxis for transplant re- cipients visiting the endemic zone is not recommended. Patients re- ceiving biological modifiers, such as tumour necrosis factor (TNF) antagonists, are probably at increased risk in endemic areas but there are no data on prophylaxis. It is recommended that these patients are screened for coccidioides by serology prior to starting therapy. FURTHER READING Ampel NM (2010). New perspectives on coccidioidomycosis. Proc Am Thorac Soc, 7, 181–5. Crum NF, et al. (2004). Coccidioidomycosis: a descriptive survey of a reemerging disease. Clinical characteristics and emerging contro- versies. Medicine (Baltimore), 83, 149–75. Fitterer C, et al. (2016). Coccidioidomycosis in patients with selected solid organ cancers: a case series and review of medical literature. Mycopathologica, 181, 787–98. Galgiani JN, et al. (2016). 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioido- mycosis. Clin Infect Dis, 63, e112–46. Lewis ERG, Bowers JR, Barker BM (2015). Dust devil: the life and times of the fungus that causes valley fever. PLoS Pathog, 11, e1004762. Limper AH, et al. (2011). An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Resp Crit Care Med, 183, 96–128. Mathisen G, et al. (2010). Coccidioidal meningitis: clinical presenta- tion and management in the fluconazole era. Medicine (Baltimore), 89, 251–84. 8.7.4 Paracoccidioidomycosis M.A. Shikanai-Yasuda ESSENTIALS Paracoccidioidomycosis is a systemic mycosis caused by dimorphic fungus Paracoccidioides spp., which is found in soil and in a variety of animals, and transmitted to humans by inhalation. This fungus is re- stricted geographically to Central and South America, where it is the most common endemic chronic human mycosis, acquired in rural and periurban areas, equally distributed among prepubescent boys and girls, but more frequent in men than women (10:1). Clinical features—manifestations range from an asymptomatic course to severe and potentially fatal disseminated disease. (1) Acute form (juvenile type)—1 to 20% of cases; presentation is with progres- sive lymphadenopathy; fever and weight loss are common; liver and spleen are usually moderately enlarged; other manifestations include mucocutaneous lesions and bone and small bowel involvement. (2) Chronic form—usually occurs in men aged 30–50 years who have worked in agricultural areas; frequently involves the lung, skin, and

8.7.4 Paracoccidioidomycosis 1365 mucous membranes (mainly pharynx, larynx, and trachea); may involve lymph nodes and adrenals, also (less frequently) intestine, spleen, bones, central nervous system (brain, cerebellum, meninges) and genitourinary system. Complications include microstomia, la- ryngeal/tracheal/bronchial stenosis, pulmonary emphysema/fi- brosis, respiratory and adrenal insufficiencies, and cor pulmonale. Diagnosis and treatment—diagnosis is made by (1) direct microscopy or culture from sputum, pus, or other lesions; (2) histopathology— silver or periodic acid–Schiff staining reveals fungal cell granulomas containing fungal cells with either proliferative and/or exudative reactions; or (3) serological testing. Treatment of mild cases is with itraconazole or sulfamethoxazole-trimethoprim; severe cases of acute or chronic disease require intravenous amphotericin B or other amphotericin formulations, followed by oral drugs. Long courses of treatment (6–36 months) are required until stabilization or dis- appearance of antibodies detected by immunodifusion or counter immunoelectrophoresis tests. Definition Paracoccidioidomycosis is a systemic granulomatous disease caused by a dimorphic fungus of the complex Paracoccidioides brasiliensis and Paracoccidioides lutzii, that mainly involves the lungs, phago- cytic mononuclear system, mucous membranes, skin, and adrenals. History The disease was first described in 1908 by Lutz, a Brazilian scientist. In 1912, Splendore classified the organism as a yeast of the genus Zymonema and, in 1928, Almeida and Lacaz suggested the name Paracoccidioides. In 1930, Almeida named the fungus Paracoccidioides brasiliensis. Formerly, the disease was known as South American blastomycosis or Lutz–Splendore–Almeida disease. In 1977, it was renamed paracoccidioidomycosis. In 2005, molecular biology ana- lyses revealed that isolates from Brazil, Colombia and Venezuela were not similar and constituted the complex Paracoccidioides brasilien sis, and in 2009 a new species Paracoccidioides lutzii was reported in North and Central area of Brazil. Epidemiology Paracoccidioidomycosis is the most common endemic human my- cosis in Latin America but is restricted geographically to Central and South America, ranging from Mexico to Argentina. The disease is prevalent in Brazil, Colombia, Venezuela, Argentina, Uruguay, Paraguay, Guatemala, Ecuador, Peru, and Mexico. Imported cases have been recorded in the United States of America, Europe, and Asia. Paracoccidioidomycosis is the eighth most important cause of mortality from chronic infectious diseases in Brazil, the highest among systemic mycoses. Recent registered data suggested epi- demic levels of disease in the North Region of Brazil. Prevalence, inferred from the result of intradermal paracoccidioidin testing, ranges from 6 to 60.6% among rural and urban populations of endemic and nonendemic areas; lower rates were observed in the same region when a more specific antigen, 43 kDa glycoprotein, was employed in comparison with paracoccidioidin. The disease is equally distributed among prepubescent boys and girls but among adults the sex ratio of clinical cases is 10 or more men to each woman. This may be explained by the ability of oestrogens to inhibit the transformation of mycelium or conidia to yeast. The disease is most common among 20- to 50-year- old agricultural workers or those who have lived in rural endemic areas. Spouses of patients are rarely affected by the disease, which suggests that hormonal and genetic factors play a part in the distribution of this my- cosis. Transmission from one person to another has not been shown. Ecology The geographical regions where paracoccidioidomycosis is most prevalent are humid with more acidic soils and a temperature range from 15 to 30°C. P. brasiliensis has been isolated from soil, animals such as armadillos, and rarely in dog food, penguin faeces, and in the intestinal contents of bats. Efforts to maintain the fungus in bat in- testines have been unsuccessful. The saprophytic habitat of P. brasil iensis has yet to be discovered. Aetiology Phylogenetic studies of eight regions in five nuclear loci of 65 P. brasiliensis isolates indicated initially that this fungus consisted of at least three distinct, previously unrecognized species: S1 (spe- cies 1 with 38 isolates from Brazil, Argentina, Paraguay,

Peru, and Venezuela isolates), PS2 (phylogenetic species 2 with five Brazilian and one Venezuelan isolates), and PS3 (phylogenetic species 3 with 21 Colombian isolates). Another phylogenetic species of P. brasiliensis, PS4, is further registered from analysis of samples of soil in Venezuela. Additionally, other Brazilian isolate 'Pb01-like' species exhibits great sequence and morphological divergence from the S1/PS2/PS3 spe- cies clade and was named as Paracoccidioides lutzii. Recently, re- naming of species of the Paracoccidoides brasiliensis complex was suggested based on divergences on nuclear gene genealogies but not found on mitocondrial genes (Turrissini et al., 2017): Paracoccidioides americana sp., formely known as "PS2"; Paracoccidioides venezuelensis sp., formely known as "PS4". Paracoccidioides restrepiensis sp., formely known as "PS3"; Paracoccidioides brasiliensis stricto sensu, previously known as "S1'. Mycology P. brasiliensis is a dimorphic fungus that can be cultivated either as a mould or a yeast. When cultured at 25°C, it appears after 15–30 days as white colonies. When Sabouraud's dextrose agar is used, the my- celium shows hyaline septate hyphae with branches. P. brasiliensis grows as a yeast in human and animal tissues (Fig. 8.7.4.1) and in cultures maintained at 37°C. Colonies can be observed after 7 to 20 days. Under direct microscopy, yeast forms are seen as oval or spherical cells with doubly refractile walls; the cells vary in size from buds of 2–10 µm in diameter to mature cells of 20–30 µm. Mother cells may produce 10–12 uniform or variably sized buds (Fig. 8.7.4.2), forming the characteristic 'pilot wheel' shape observed in biological samples or in infected tissues.

section 8 Infectious diseases 1366 Conidia produced by mycelium represent the infectious form and are inhaled through the respiratory tract. Analysis of 6022 assembled groups from mycelium and yeast phase expressed sequence tags of about 80% of the estimated genome of P. brasiliensis. The transcriptome analysis reported information about sequences related to the cell cycle, stress response, drug resist- ance, and signal transduction pathways of the pathogen. Virulence Virulence, defined as the ability to produce disseminated infection in experimental animals, varies between different fungal isolates but little is understood of the biochemical basis for these differences. The pres- ence of higher levels of α-1,3-glucan in virulent strains of P. brasilien sis compared with avirulent strains was initially related to virulence, but no correlation has been shown between glucans and virulence in experimentally induced infections. Binding of laminin to yeast cells (possibly through binding to gp43) enhanced their pathogenicity in the hamster testicle model. However, in a murine model, previous treatment of laminin with high and low virulent isolates of P. brasilien sis showed lower inflammatory responses with the virulent isolate and decreased pulmonary fungal burden with the low-virulence isolate, suggesting an inhibitory effect of laminin treatment on P. brasiliensis infectivity. More recently the importance of a 32 kDA hydrolase from P. brasiliensis during initial adherence to host cells has been reported. Pathogenesis Experimental and clinicopathological observations indicate that the respiratory route is the main portal of entry and the lung is the pri- mary site of infection. The first fungus–host contact occurs through inhalation of airborne conidia. When mice are experimentally infected through the respira- tory route, conidia have been observed in the alveoli soon after inocu- lation. Some 12–18 h after the exposure, yeast forms can be observed in the alveoli. There is an initial inflammatory response, which is me- diated by polymorphonuclear cells, followed by granuloma formation. The primary infective complex develops at the inoculation site and in- volves the surrounding lymphatic vessels and regional lymph nodes. The fungus spreads to other parts of the lung through peribronchial lymph- atic vessels and drains into regional lymph nodes. Haematogenous dis- semination to a variety of organs and tissues can occur at this time. The lesions usually undergo involution and the fungi remain dormant if the host's immune response can control their proliferation. A balanced

host–fungus relationship is associated with the absence of symptoms, although, in some children or young adults, acute disease might arise, primarily affecting the phagocytic mononuclear system. In adult life, previously quiescent lesions can become reactivated, especially in the lungs, leading to the adult or chronic form of the disease. Pathology The characteristic lesion is a granuloma containing P. brasiliensis cells. The infected tissue might exhibit a predominantly prolifera- tive, granulomatous inflammatory response and/or an exudative re- action, sometimes resulting in necrosis, with variable numbers of neutrophils and large numbers of extracellular yeast cells, leading to a chronic epithelioid granuloma. Autopsy studies, mainly of adult patients, indicate that the or- gans most frequently involved are the lungs (42–96%), adrenals (44–80%), lymph nodes (28–72%), pharynx/larynx (18–60%), and skin/other mucosal surfaces (2.7–64%). Host–fungal interaction Nonspecific immune response The influence of genetic factors on the individual susceptibility to this mycosis is suggested by the observation of higher rates of HLA phenotypes A9, B13, B40, and Cw3 among patients than in con- trols and higher rates of HLA DRB1*11 in patients with unifocal disease than with other forms of the disease. Analysing cytokine polymorphisms, the AA genotype of IL12RB1 was more frequent in the disseminated chronic disease in comparison to patients with unifocal chronic disease. In isogenic mice, resistance to P. brasilien sis is controlled by a single autosomal gene. The ability of circulating human neutrophils, obtained by bronchoalveolar washing, to digest the yeast forms of fungi was im- paired in severe cases, while this defect was absent in uninfected family members of patients. Interaction between a glycoprotein of 43 kDA of the fungus and monocytes was shown to modulate the expression of TLR2 (by inducing IL10 production), TLR4 (inducing TNFα secretion) and mannose receptors. Fig. 8.7.4.1 Small and large yeast forms of Paracoccidioides brasiliensis in the lung of a transplant recipient (methenamine silver stain). Courtesy of C. S. Lacaz. Fig. 8.7.4.2 Scanning electron micrograph of a multiple budding yeast cell of Paracoccidioides brasiliensis. Courtesy of C. S. Lacaz.

8.7.4 Paracoccidioidomycosis 1367 Specific immune response Host–fungal interaction in infection and disease was analysed through in vivo intradermal tests for ubiquitous fungal antigens, in vitro lymphoblastic transformation tests, and intra- and extracel- lular cytokine secretion, chemokines, and regulatory T-cell activity after stimulation with mitogens or P. brasiliensis antigens (PbAg). Infected people (asymptomatic individuals without disease) showed a positive skin test to PbAg, absence of specific antibodies, a vigorous lymphoproliferative response to PbAg, and a typical T-helper (Th) type 1 pattern of cytokines (see Table 8.7.4.1). They had a higher ex- pression of CD80 monocytes and lower expression of CD86 mono- cytes compared to patients with chronic or acute disease. Patients with acute disease showed impairment of proliferative response to PbAg and a mixed Th2/Th9 cytokine pattern. This pattern is asso- ciated with poor granuloma formation, spreading of the fungus and high levels of antibody production (immunoglobulins IgG 1, IgG 4, and IgE). Patients with chronic disease present a predominant Th17/ Th22 response. The specific lymphoproliferative response was lower than in asymptomatic paracoccidioidomycosis-infected patients but higher than in patients with acute disease (see Table 8.7.4.1). More recent research indicates that regulatory T cells exhibiting suppressive activity in patients' cells seem to play a role in control- ling local and systemic immune responses. In biopsies of mucosa and skin lesions, Foxp3+ cells were shown in compact granulomas sug- gesting their role in the modulation of the local immune response. The presence of IL17 in mucosa and skin lesions also suggests that this cytokine plays a role in cutaneous and mucosal lesions, perhaps in the clearance of the fungal antigens. In mice, treatment of dendritic cells with gp43 plus lipopolysac- charide was followed by

an increase of fungal colony forming units in the lungs in comparison with controls, suggesting that gp43 might reduce effectiveness of the immune response in the primary infec- tion. In pulmonary murine paracoccidioidomycosis, a dual role of interleukin 4 (IL-4, a Th2 cytokine) was observed in IL-4-depleted mice depending on the host genetic pattern: isogenic resistant mice showed better control of the disease. Conversely, susceptible mice showed enhanced pulmonary infection, suggesting a role for IL-4 in the modulation of immune response, not only as a Th2 cytokine. Antibodies may enhance phagocytosis through opsonization of the fungus, but their role in resistance is not established. The im- portance of late hypersensitivity in protection has been observed recently in patients receiving cytotoxic therapy for associated neo- plasms and in those with AIDS presenting severe disease. Clinical features The range is from an asymptomatic course to severe and potentially fatal disseminated disease. The incubation period is unknown except in a laboratory worker, who developed a skin lesion some days after an accidental inoculation. The disease has been reported in children 3 years of age or older who had lived for some years in the endemic area. A proposed classification of clinical forms of paracoccidioidomycosis is shown in Box 8.7.4.1. Localization in a particular tissue or organ and the degree of se- verity of the disease according to established criteria make this clas- sification easily and uniformly applicable. General and nutritional debility and organ dysfunction (lung, brain, adrenals, bone marrow) indicate the severity of the disease. In immunosuppressed patients, signs of chronic and acute disease are observed simultaneously, with dissemination of fungi through phagocytic mononuclear cells. Acute form (juvenile type) Children, adolescents, and young adults (under 30 years of age) are affected, men and women equally. Only 1–20% of patients fall into this group. There is progression for 2 or 3 months or longer, char- acterized by involvement of the phagocytic mononuclear system. Cervical, axillary, and inguinal nodes are the most commonly en- larged (Fig. 8.7.4.3). Nodes are initially hard but are sometimes fluc- tuant and drain pus rich in fungi. Less frequently, deep-seated lymph nodes can also be affected. When the hepatic perihilar lymph nodes are enlarged, they sometimes produce symptoms of obstructive jaundice. The liver and spleen are usually moderately enlarged. Bones (clav- icle, scapulae, ribs, skull, long, and flat bones) and, rarely, the bone marrow may be involved. Radiographs show lytic lesions without periosteal reaction. Involvement of the small bowel may be asymp- tomatic or produce abdominal pain, diarrhoea, constipation, and even intestinal obstruction. Radiological studies of the digestive tract reveal intestinal tract involvement in about 50% of clinical cases. Fever and weight loss are common. Multiple mucocutaneous lesions are more frequent in some geographical areas (Fig. 8.7.4.4). High transient blood eosinophilia (up to 30 000/mm3) has some- times been described. Clinical lung involvement is rarely described in this form of paracoccidioidomycosis. In some case reports, either bronchopneu- monia or primary complex-like disease have been observed. Table 8.7.4.1 Host–fungal interaction in paracoccidioidomycosis: cytokine secretion and P. brasiliensis antigenaemia/antigenuria in infection and disease Groups Cytokine secretion and antigenaemia/antigenuria Intracellular cytokines Infectiona IFγ, Ab undetectable IFγ↑, TNFα↑, IL-2↑ Acute disease IFγ↓, IL-4↑↑, IL-5↑↑, IL9↑,
IL21↑, IL-10↑, Ab↑ (IgG 4), antigenaemia/antigenuria↑ IFγ↓, TNFα↓, IL-2↓ Chronic disease IFγ↓, IL-4↑, IL-5↑, IL-10↑, Ab↑
(IgG 2), IL17↑,IL22↑ IL17 in mucosa and skin biopsies, Foxp3 in compact granulomas IFγ↓, TNFα↓, IL-2↓ Immunosuppressed patients ? IFγ↓, IL-10↑,? IL-4,? IL-5↓, Ab increased or lower levels, antigenaemia/antigenuria ↑ ?b Ab, antibodies; IF, interferon; IL, interleukin; TNFα, tumour necrosis factor α; ↓, decrease; ↑, increase. a Asymptomatic individuals sensitized by P. brasiliensis antigens without signs and symptoms. b Decrease in lymphoproliferation in response to P. brasiliensis

antigens: intracellular cytokines unknown. Box 8.7.4.1 Paracoccidioidomycosis: proposed classification of clinical forms • Paracoccidioidomycosis infection • Regressive (self-healing) paracoccidioidomycosis • Paracoccidioidomycosis disease — Acute form (juvenile type)—moderate or severe — Chronic form (adult type)—mild, moderate, or severe • Sequelae

section 8 Infectious diseases 1368 Chronic form This form of the disease usually occurs in 30- to 50-year-old men who have worked in agricultural areas. The male to female ratio varies from 10:1 to 25:1. The evolution is insidious and, in many cases, clinically mild. The organ most frequently involved is the lung, followed by skin and mucous membranes, mainly pharynx, larynx, and trachea. Lymph nodes and adrenals might be compromised. More than one organ or tissue is usually involved. Less frequently, intestine, spleen, bones, cen- tral nervous system (brain, cerebellum, meninges), eyes, genitourinary system, myocardium, pericardium, and arteries are involved. The patients might be asymptomatic or complain of dyspnoea, cough, sometimes purulent sputum, and, rarely, haemoptysis. Fever is unusual. Physical examination is frequently normal or there can be scattered rales. In contrast, chest radiography commonly reveals bilateral, asymmetrical, reticulonodular infiltrates in the middle and lower parts of the lungs (Fig. 8.7.4.5). Apical cavities and pleural ef- fusions are less frequently observed. Fig. 8.7.4.3 Lymph node and skin involvement in a patient with the acute form of paracoccidioidomycosis. Courtesy of C. S. Lacaz. Fig. 8.7.4.4 Multiple molluscum-like lesions in a young Peruvian patient. Copyright Francisco Bravo, Lima. Fig. 8.7.4.5 Alveolar and interstitial infiltrates in both lungs in a patient with chronic paracoccidioidomycosis. Department of Infectious and Parasitic Diseases, School of Medicine, University of São Paulo. Fig. 8.7.4.6 Mucocutaneous lesions in a patient with chronic paracoccidioidomycosis. Courtesy of C. S. Lacaz. Fig. 8.7.4.7 Disseminated skin lesions. Courtesy of Universidad Peruviana Cayetano Heredia.

8.7.4 Paracoccidioidomycosis 1369 Cutaneous lesions include papules, pustules, ulcers, crusted ul- cers, vegetations, tuberculoids, verrucoids, or acneiform lesions mainly on the face (Fig. 8.7.4.6) or limbs. Multiple, scattered le- sions result from haematogenous dissemination (Fig. 8.7.4.7). Subcutaneous cold abscesses, more commonly associated with bone lesions, can occur. Mucosal lesions are usually in the mouth and/or oropharynx, including the palate (Fig. 8.7.4.8), uvula, and tonsils, or in the re- spiratory tract, involving mainly the larynx (vocal cords, glottis, and epiglottis) and trachea. Pain is usually intense and might hamper mastication and swallowing. Hoarseness and dysphonia result from laryngeal lesions and can lead to obstruction of the upper respira- tory tract. Examination shows ulcerative, verrucous, vegetant, and infiltrative ‘moriform’ stomatitis, resembling a raspberry, with pap- ules, vesicles, and haemorrhagic spots. The last is characteristic of this mycosis and appears as shallow ulcers, with a granular surface showing multiple, fine, haemorrhagic points. Few lymph nodes are involved, in contrast to the acute form of the disease. Uni- or bilateral lesions in the adrenal glands have been found in about half of patients coming to autopsy. Partial adrenal insuffi- ciency has been documented in about 40% of the cases but only 7.4% were symptomatic. Concomitant tuberculosis is observed in about 10–15% of cases of pulmonary paracoccidioidomycosis and has also been described in cases of lymph node involvement by P. brasiliensis. Carcinomas may arise in pulmonary or mucosal mycotic lesions. Sequelae Nowadays, sequelae constitute one of the most important problems in the management of paracoccidioidomycosis. Although fungal multiplication can be controlled by chemotherapy, impairment of vital functions might prove fatal. Acute form Inflammmatory lesions in the small intestine and mesenteric lymph nodes can result in fibrosis, causing lymphatic obstruction,

intestinal malabsorption, or protein-losing enteropathy. A clinical picture of severe malnutrition and immunodeficiency has been re- ported (Fig. 8.7.4.9). Chronic form As the lesions usually tend to heal by fibrosis, sequelae such as microstomia and laryngeal, tracheal, or even bronchial stenosis might be observed. Corrective surgery is indicated. Pulmonary emphysema, fibrosis, respiratory insufficiency, and, finally, cor pulmonale are frequent sequelae. Obstructive and re- strictive patterns of ventilatory defect have been found in about 36 and 16% of patients, respectively. As many as 30% of these pa- tients might die as a result of respiratory or cardiorespiratory failure. Adrenal reserve is decreased in 15–50% of patients and there is cen- tral nervous system dysfunction in about 6–25% of patients. Diagnosis Microbiological identification Isolated or budding (single or multiple) mother cells are observed under direct microscopy in sputum, pus from lymph nodes, and ma- terial from the skin or mucous membrane lesions. Specimens are cultured at 37°C on blood, chocolate, or yeast ex- tract agar. The colonies are produced after 7 days, usually in 10 to 20 days. Cultures can be maintained at 25°C on Sabouraud's dextrose agar, where the colonies might be noticed after 15 to 30 days. Histopathology Silver or periodic acid–Schiff staining is required to detect the fungus in sputum. Diagnostic features are the variable size (1–30 μm) of the yeast cells, and their multiple budding. Proliferative or exudative re- actions, as described in the section on pathology, may be observed. Immunological tests Serological reactions Immunodiffusion (Ouchterlony) and counterimmunoelectrophoresis are the best techniques initially. Sensitivities and specificities are as Fig. 8.7.4.8 Palatal lesion. Copyright D. A. Warrell. Fig. 8.7.4.9 Ascites, cachexia, and immunodeficiency due to malabsorption and protein-losing enteropathy as sequelae of acute paracoccidioidomycosis. Courtesy of M. Shiroma.

 high as 95%. Cross reactions are mainly with other systemic mycoses such as histoplasmosis, aspergillosis, cryptococcosis, and candidiasis. Complement fixation and indirect immunofluorescence are less reliable tests for diagnosis and have not been employed even for treatment follow-up. Recently, enzyme immunoassays employing PbAgs, including a 43 kDa glycoprotein, have shown high sensitivity and specificity. Antibody titres tend to decrease about 3 to 6 months after starting specific therapy and to disappear after 9 months to 5 years or more. For diagnosis of paracoccidioidomycosis in Central and North regions of Brazil, it has been shown that the sensitivity of immuno- diffusion or counterimmunoelectrophoresis is only appropriate when antigens from local isolates were employed. This sensitivity is lower than 40% when antigens classically employed for other re- gions were used, indicating differences in antigenic composition of Paracoccidioidodes species from isolates of these regions. However, antigenic preparations without cells derived from P. lutzii have been able to diagnose by immunodiffusion test 100% of sera from patients with paracoccidioidomycosis due to P. lutzii. Antigenaemia and antigenuria have been considered useful in- dications in patients presenting low levels of antibodies in the sera, both for diagnosis and follow-up after treatment, particularly in an immunocompromised host. Circulating gp43 and gp70 antigens were detected in 100% of cerebrospinal fluid and almost all serum samples of patients with neuroparacoccidioidomycosis. The correlation between immunological and histopathological findings and clinical forms is outlined in Table 8.7.4.1. Treatment Clinically active disease is usually treated for 6–36 months, according to the severity of the disease, until disappearance of antibodies detected by immunodiffusion or counterimmunoelectrophoresis tests or their stabilization at low levels (1:2 and 1:4, respectively) in test performed 6 months apart. In mild or moderately severe cases, co-trimoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole, twice or three times a day) or imidazoles (itraconazole 100–400 mg/day) have been shown to be effective. In a randomized trial with 42 cases, sulphadiazine (150 mg/kg per day), itraconazole (50–100 mg/day), and ketoconazole

(200–400 mg/day) were equally effective in pa- tients with moderately severe disease. More recently, a study of 177 cases found no difference in the efficacy and effectiveness of initial treatment of 47 individuals given itraconazole compared with 130 given sulfamethoxazole–trimethoprim, but the time to clinical cure was shorter in those given itraconazole (105 vs. 159 days), specifically in patients with the chronic form of the disease. Voriconazole has been used in a randomized study in comparison with itraconazole with similar results and, since it achieves high levels in cerebrospinal fluid, it could be useful in neuroparacoccidioidomycosis. Severe cases of acute or chronic disease should be treated with intravenous infusion of amphotericin B. Both amphotericin B and liposomal amphotericin preparations are employed during a short induction phase, aiming to control the evolution and dissemination of the lesions, and should be replaced by maintenance therapy as soon as signs of clinical improvement are achieved. The daily dose of amphotericin begins at 0.1–0.2 mg/kg, increasing up to 1.0 mg/kg, with the total dose ranging from 1 to 3 g or more. Toxic reactions to amphotericin B include fever, chills, headache, anaemia, and nephro- toxicity characterized by tubular acidosis and potassium urinary excretion and resultant hypokalaemia and azotaemia. In most cases, these reactions can be controlled until the end of the course of therapy. Co-trimoxazole (80 mg of trimethoprim and 400 mg of sulphamethoxazole), twice a day, or itraconazole (100–200 mg/day) are recommended as maintenace therapy. Liposomal amphotericin has been used in severe cases of paracoccidioidomycosis, but a short period of treatment was followed by relapses. In a Brazilian study, relapses were seen in 5.2% of 400 registered cases, most of them in the chronic form (71.4%). Prognosis Even though the disease is easily controlled in most cases, the course of treatment is long and abandonment of treatment is the most important cause of therapeutic failure, e.g. in Brazil. Normalization of cellular specific responses, particularly of the skin test (paracoccidioidin) indicates a good prognosis. Death may occur in severe acute or chronic cases and severe cases with sequelae. FURTHER READING André DC, et al. (2004). Binding of laminin to Paracoccidioides brasilien sis induces a less severe pulmonary paracoccidioidomycosis caused by virulent and low-virulence isolates. Microbes Infect, 6, 549–58. Bocca AL, et al. (2013). Paracoccidioidomycosis: eco-epidemiology, taxonomy and clinical and therapeutic issues. Future Microbiol, 28, 1177–91. Borges-Walmsley MI, et al. (2002). The pathobiology of Paracoccidioides brasiliensis. Trends Microbiol, 10, 80–7. Calich VLG, et al. (1985). Susceptibility and resistance of inbred mice to Paracoccidioides brasiliensis. Br J Exp Pathol, 66, 585–94. Cavalcante RS, et al. (2014). Comparison between Itraconazole and Cotrimoxazole in the Treatment of Paracoccidiodomycosis. PloS Neglected Trop Dis, 8, e2793. de Castro LF, et al. (2013). Characterization of the immune response in human paracoccidioidomycosis. J Infect, 67, 470–85. Hollanda FMC, et al. (2016). Polymorphisms on IFNG, IL12 and IL12RB1 genes and paracoccidioidomycosis in the Brazilian popu- lation. Infect Genet Evol, 43, 245–51. Matute DR, et al. (2006). Cryptic speciation and recombination in the fungus Paracoccidioides brasiliensis as revealed by gene genealogies. Mol Biol Evol, 23, 65–73. Pagliari C, et al. (2011). Paracoccidioidomycosis: cells expressing IL17 and Foxp3 in cutaneous and mucosal lesions. Microb Pathog, 50, 263–7. Shikanai-Yasuda MA (2005). Pharmacological management of paracoccidioidomycosis. Expert Opin Pharmacother, 6, 385–97. Shikanai Yasuda MA (2017). Brazilian guidelines for the clinical management of paracoccidioidomycosis. Rev Soc Bras Med Trop, 50, 715–40. Teixeira MM, et al. (2009). Phylogenetic analysis reveals a high level of speciation in the Paracoccidioides genus. Mol Phylogenet Evol, 52, 273–83. Turissini DA, et al. (2017). Species boundaries in the human pathogen Paracoccidioides. Fungal Genet Biol, 106, 9–25.

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