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Primary Cutaneous Coccidioidomycosis in an Italian Nun Working in South America and Review of Published Literature

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Abstract Coccidioidomycosis is a systemic disease caused by the dimorphic fungus *Coccidioides,* endemic in parts of the Southwestern USA and Central and South America. Two species, *Coccidioides immitis* and *Coccidioides posadasii*, were differentiated. Primary cutaneous coccidioidomycosis (PCC) has been reported rarely. An unusual case of PCC characterized by a persistent solitary lesion diagnosed in Italy in an immunocompetent Italian nun living in Argentina is described. The isolate was identified by sequence analysis as *C. posadasii.* Antibody screening was negative. A total of 39 cases of PCC have been reported in the literature. Infections occurred as a consequence of traumatic implantation in a natural setting in endemic areas or of accidental inoculation in laboratory workers. Importance of accurate investigation of travel history and of occupational hazards to laboratory workers is outlined.

Keywords Cutaneous mycoses · *Coccidioides posadasii* · Coccidioidomycosis · Imported mycoses

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Introduction

Coccidioidomycosis is a systemic disease caused by the dimorphic fungus *Coccidioides,* endemic in parts of the Southwestern USA and Central and South America [1].

In 2002, on the basis of genomic analysis, the genus *Coccidioides* was differentiated into two species: *Coccidioides immitis* including isolates from California and *Coccidioides posadasii* including isolates from outside of California [2, 3].

Inhalation of arthroconidia is the common route of infection and can result in a pulmonary infection, often self-limited. Dissemination occurs in approximately 1 % of infections [1]. Primary cutaneous coccidioidomycosis (PCC) has been reported rarely.

We report an unusual case of PCC diagnosed in Italy.

Case Report

A 56-year-old immunocompetent Italian nun living in Argentina has been suffering from a 4-year-persistent

erythematous papular plaque on the right cheek. The lesion appeared in September 2000 as brown, lenticular, itching macula, progressively thickened and evolved into a papule (December 2000). The lesion progressively increased in size but ceased to itch. From 2002 to 2005, several histological examinations were performed in different American countries with diverse diagnoses: sarcoidosis resulting in a 6-month steroid therapy with deterioration of the lesion, lupus vulgaris, leishmaniosis, squamous carcinoma and cutaneous coccidioidomycosis, resulting in a one-year therapy with itraconazole (100 mg/die) without improvement.

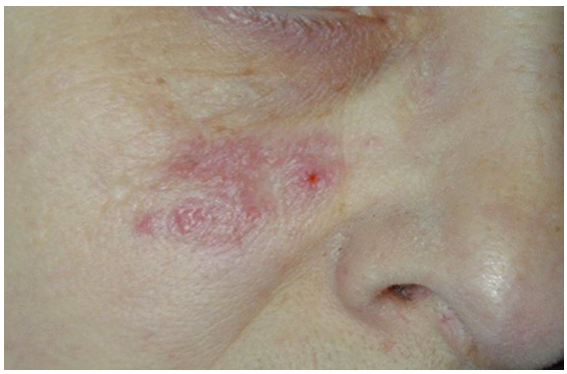

Fig. 1 Erythematous papular plaque 3 × 1.5 cm in size, irregular and oval with a central scar due to previous biopsies

In January 2005, while she was in Italy, the patient was admitted to the Dermatology Department of IRCCS Ospedale Maggiore Policlinico. At the time of admission, the lesion appeared as an erythematous papular plaque 3 × 1.5 cm in size, irregular and oval with a central scar due to previous biopsies (Fig. 1). No other symptoms were present. Lymph nodes were not detectable. The patient was otherwise in good health. She did not remember any previous skin trauma, respiratory symptoms, headache or fever. A punch biopsy was performed.

Histopathology revealed a diffuse inflammatory infiltrate in the dermis and two small granulomas. A characteristic spherule of 30 μm in diameter, containing eosinophilic endospores (2 μm) within a multinucleated giant cell, and fragments of fungal walls within a granuloma were observed (Fig. 2).

White, cottony colonies grew in culture after one week at 30 °C. Microscopically, hyaline, septate hyphae and abundant barrel-shaped arthroconidia

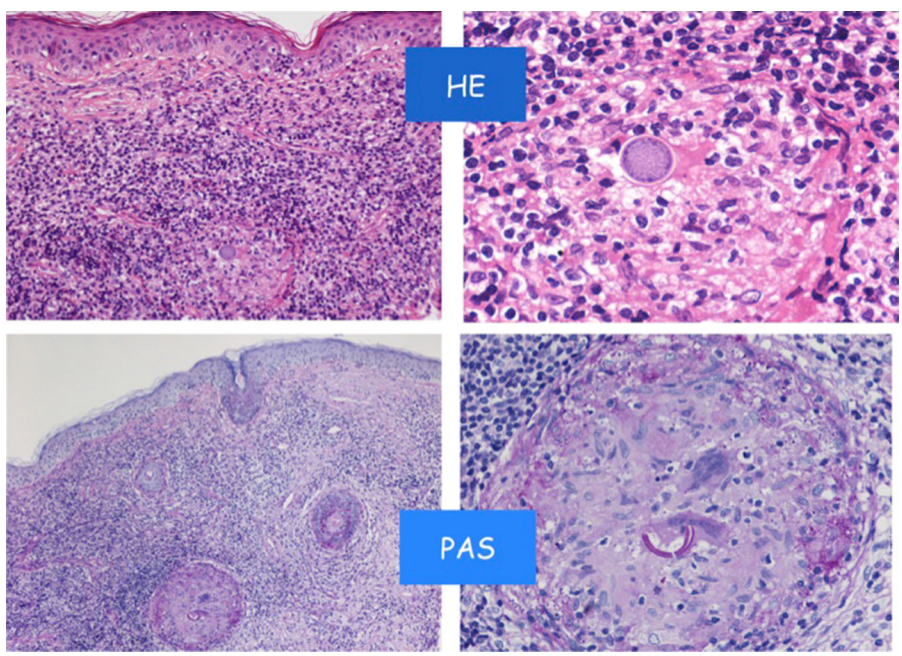

Fig. 2 Histopathology of the punch biopsy: hematoxylin–eosin (HE) and periodic acid–Schiff (PAS). Diffuse inflammatory infiltrate in the dermis (lymphocytes and monocytes) and two small granulomas. A characteristic spherule of 30 μm in diameter containing eosinophilic endospores (2 μm) within a multinucleated giant cell and fragments of fungal walls within a granuloma

Table 1 Characteristics of cases of primary cutaneous coccidioidomycosis reported in the literature

Year of report and first authors	Geographical/ occupational exposure	Patient's sex—age (years)	Patient's activity (inoculation route)	Site of infection	Clinical features	Treatment and outcome
1927 [9][a]	USA–California	M—36	n.a. (inoculation by cactus thorn)	R thumb	Ulcer with LAN and LAD → dissemination to knees and thigh	Roentgen rays and antimony K tartrate → resolution
1933 [10][a]	USA–California	M—26	Studio stagehand (n.a.)	R arm	Abscess with LAD	Radical resection and cautery → resolution
1953 [6][a]	USA–California embalmer	M—32	Embalmer (skin abrasion)	R finger	Ulcerated nodule with LAN and LAD	Excision and drainage of axillary LN → resolution
1956 [11][a]	Laboratory	F—29	Laboratory worker (accidental inoculation)	L finger	Ulcerated nodule with LAN and LAD	Excision → nodule lesion resolution and persistence of LAD
1959 [12][a]	Laboratory	M—34	Laboratory worker (accidental inoculation)	L finger	Ulcerated nodule with LAN and LAD	None → nodule lesion resolution and persistence of LAD
1961 [13][a]	Laboratory	M—??	Laboratory worker (accidental inoculation)	Wrist bone	Osteomyelitis	Excision → resolution
1963 [14][a]	USA–Arizona	M—18	Holidays in Arizona (inoculation by cactus thorn)	L thigh	Ulcer with LAD	None → resolution and persistence of LAD
1963 [15][a]	USA–Arizona	M—22	Farmer (inoculation by barbed wire)	L foot	Ulcer with LAN and LAD	Excision → resolution
1964 [16][a]	Laboratory	M—49	Laboratory worker (accidental inoculation)	L finger	Nodule with urticaria	Excision → resolution
1964 [17][a]	Laboratory	M—29	Laboratory worker (inoculation by thorn)	Finger	Ulcer with LAN	None → resolution
1964 [17][a]	Laboratory	M—32	Laboratory worker (accidental inoculation)	Thenar eminence to bone	Abscess with LAD and osteomyelitis	Bivalved cast with saline irrigation and bone graft → resolution
1964 [17][a]	Laboratory	M—26	Laboratory worker	L wrist	Necrotic papule with LAD	Local AMB (22 d) then excision and debridement → resolution
1965 [18][a]	USA–California	M—61	Farmer (grapevine scratch)	Scalp	Ulcerated nodule with LAD	Excision and iv AMB (6 w) → resolution
1965 [18][a]	USA–California	M—59	Farmer (grapevine scratch)	R cheek	Ulcerated plaque with LAD	None → resolution
1965 [19][a]	USA–California	F—12	n.a. (splinter laceration)	R foot	Abscess with LAD and erythema nodosum	AMB os (5 w) and cauterization of inguinal LN and foot lesion and UV light → resolution

Table 1 continued

Year of report and first authors	Geographical/ occupational exposure	Patient's sex—age (years)	Patient's activity (inoculation route)	Site of infection	Clinical features	Treatment and outcome
1965 [19][a]	USA–California	F—3	n.a. (splinter laceration)	L hand	Abscess with LAD and sinus tract formation in axilla	Excision, LN drainage and topical AMB → resolution at 26 mos
1965 [19][a]	USA–California	F—13	n.a. (barbed wire laceration)	R hand	Nodule with LAD followed by meningitis	Atrioventricular shunt and i.t. and iv AMB → after 11 mos still requires i.t. ABM therapy
1967 [20]	USA–California	M—43	Farmer (corneal abrasion following dust storm)	L cornea	L eye keratitis → uveitis	AMB iv, eye enucleation → cured
1976 [21]	Clinic	F—25	Physician (inoculation with infected needle)	L hand, finger	Abscess with LAN and LAD	Iv AMB (17 days) and local AMB (5 mg/day per 70 days) → resolution
1977 [7][a]	Laboratory	F—31	Laboratory worker (accidental inoculation by splinter)	L index finger	Nodule with pus from a sinus tract into proximal phalanx	Excision and cannulation with AMB irrigation of sinus tract → resolution
1981 [22]	USA–Arizona	M—83	Working in his yard in Arizona (n.a.)	Scalp	Hyperkeratotic nodule	Ketoconazole →??
1986 [23]	USA–Texas	M—7	Cut from broken bottle in natural environment attending a cock fight	R hand	LAD of arm and axilla (2 w later)	AMB iv (2 w) followed by ketoconazole (? w) → resolution
1987 [24]	Laboratory	F—62	Laboratory worker (accidental inoculation)	L finger	Papule, fistula, LAD, arthromyalgia, exanthema	Ketoconazole and AMB → resection
1988 [25]	USA–Nebraska	M—30	No data available	Lower lid region	Chronic erythematous infection, cutaneous eruption	not reported
1994 [26][a]	USA–California	M—27	n.a. (wart traumatized by the pt with wood splinters and needle)	R foot (plantar)	Pruritus and pain followed by exudative ulcer	Itraconazole (200 mg/day) → resolution at 3 mos
2002 [27]	USA–Arizona	M—50	Businessman visiting Arizona (n.a.)	R periorbital region	Two granulomatous nodules studded with pustules	Itraconazole (200 mg × 2/day for 3 mos) then 200 mg/day after improvement
2003 [28]	USA–Ohio	F—28	Guardswoman in Ohio (bug bite)	L forearm	Nodule	Excision → resolution
2006 [29]	Mexico	F—19	Mexican (trauma with fingernails)	Tip of the nose	Elevated nodule with verrucous aspect	Itraconazole 400 mg/d for 12 mos → resolution after 6 mos
2009 [30]	USA–Arizona	F—37	Veterinary assistant (cat bite)	R hand	Erythema, swelling, lymphangitis	Fluconazole 2 mos → resolution

Table 1 continued

Year of report and first authors	Geographical/ occupational exposure	Patient's sex—age (years)	Patient's activity (inoculation route)	Site of infection	Clinical features	Treatment and outcome
2010 [31]	USA–New Mexico	M—77	Puncture from a mosquito branch (New Mexico)	L lower back	Thin pink papule (6 × 8 mm)	Excision → resolution
2012 [32]	Mexico	M—35	Teacher in rural area (Mexico) trauma probably with fingernails	L preauricular region	Elevated nodule (2 cm)	Surgical removal + itraconazole 400 mg/day for 4 mos → cure
2012 [32]	Mexico	M—65	Goat farmer in rural desert area (Mexico)	L preauricular region	Fluctuating abscess (plus palpable adenopathies in the neck)	Surgical removal + itraconazole 400 mg/day for 6 mos → cure
2012 [32]	Mexico	F—32	Vacation in rural areas (Mexico)	Nose and cheeks	Erythematous papules and small ulcers	Itraconazole 400 mg/day for 4 mos → cure
2012 [32]	Mexico	M—68	Farmer (Mexico) injury with barbed wire	L hand	Small suppurative micronodular lesions (dorsum and side of hand)	Itraconazole 400 mg/day for 8 mos → cure
2012 [32]	USA–California	M—38	Farmer in Mexico trauma with cactus thorn in California	L forearm	Verrucous plaque (2 × 2 cm)	Itraconazole 300 mg/day for 10 mos → cure
2012 [33]	Mexico	M—9	Trauma with a log	Foot	Chancriform lesion and inguinal lymph node enlargement	Ketoconazole 200 mg/day for 6 mos → cure
2014 [34]	Venezuela	M—14 (mos)	Infant living in rural area (Venezuela) trauma	R eye and parathyroidea region	Violet erythematous nodule (2 cm)	Itraconazole 100 mg/day for 6 mos
2014 [35]	USA–California	M—62	Teacher in rural area (Mexico)	Neck and R axillary region	Multiple discharging sinuses	Fluconazole 400 mg/day for 4 w → healing
2014 [36]	USA–Illinois	M—33	Emigrated (5 y ago) from Guatemala; meatpacker in Chicago (inoculation of animal material from endemic regions)	L eyelid	Ulcerated nodule (1.7 cm in diameter)	Itraconazole 400 mg/day for 10 w lesion decreased in size
Present case	Argentina	F—56	Nun in South America (no memory of trauma)	R cheek	Erythematous papular plaque started as lenticular, itching macula 5 y before	Lost to follow-up

L left, *R* right, *LAN* lymphangitis, *LAD* lymphadenitis, *n.a.* not available, *y* years *mos* months, *w* weeks, *AMB* amphotericin B, *i.t.* intratecal

[a] This report has also been discussed by Chang et al. [28]

were observed, highly suspicious of *Coccidioides*. The isolate was identified as *C. posadasii* (100 %) by a broad-range PCR assay for amplification of the internal transcribed spacer (ITS) regions of rDNA and by sequence analysis within the internal GenBank of reference strains [3]. The sequence was deposited in NCBI GenBank (http://www.ncbi.nlm.nih.gov/genbank/) with the accession number KR109218. Antibody screening (complement fixation test, immunodiffusion test and IgM/IgG western blot) was negative.

Unfortunately, the patient was lost to follow-up.

Discussion

Coccidioidomycosis is a disease with a broad spectrum of clinical manifestations that can affect both immunocompetent and immunocompromised individuals. It is caused by a fungus distributed in the arid regions of the Southwestern USA, Mexico and Central and South America. Our otherwise healthy patient from Italy had lived in Argentina, known for endemic zones of *C. posadasii*. Only two cases of pulmonary coccidioidomycosis have been reported in Italians so far, who acquired their infection after a stay in Arizona/California and in Venezuela, respectively [4, 5].

Cutaneous manifestations of coccidioidomycosis most commonly occur due to dissemination. PCC does occur, but it is rare. In 1953, Wilson et al. [6] formulated criteria for documentation of PCC, namely no history of pulmonary disease immediately preceding the appearance of the cutaneous lesion, a history suggestive of traumatic inoculation, a relatively painless, indurate nodule or plaque with central ulceration and local lymphadenitis/lymphangitis.

Serology may be useful in differentiating PCC from disseminated disease. PCC may be associated with the presence of IgM coccidioidal antibodies early in the course of the disease, while IgG antibodies can rarely be detected or not at all. In contrast, the disseminated disease in immunocompetent patients is associated with high levels of specific IgG antibodies [7, 8].

To our knowledge, only 39 human cases of PCC, including the present one, have been described (Table 1). Most cases occurred as a consequence of traumatic percutaneous implantation in a natural setting in endemic areas, but several cases are secondary to accidental inoculation in laboratory workers [6].

Despite the usefulness of Wilson's criteria in defining PCC cases, some findings are not always documentable, as patients, like in our case, often come to observation several months after the lesion developed, do not remember a trauma or do not display regional lymphadenitis.

The most common lesions of PCC were verrucous plaques or granulomatous nodules; lesions resembling acne papules, rosacea, warts or skin cancer have also been described. Diagnosis was done by histological examination of tissue biopsy in all cases, and *Coccidioides* was frequently cultured.

In general, the prognosis of PCC is excellent, although diagnosis and treatment can take years, like in our case. Resolution has been reported in almost every case: by spontaneous healing or after surgical excision followed or not by antifungal treatment. Nevertheless, regardless of the relatively low dosage of itraconazole which our patient had already received for one year, a serum level of itraconazole during systemic treatment is recommended, which was not documented in our patient. So it remains open whether the dosage had been inadequate or the serum level did not reach a promising therapeutic level.

Physicians, including dermatologists, should consider coccidioidomycosis in patients returning from travels in or emigrating from endemic areas. In addition, they have to alert the laboratory workers about the clinical suspicion so that appropriate precautions are taken, such as handling specimens and cultures with extreme care only in biosafety cabinets, sealing plates accurately and not setting up slide cultures.

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