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FUNGAL INFECTIONS OF SKIN AND SUBCUTANEOUS TISSUE (A BONIFAZ AND M PEREIRA, SECTION EDITORS)

Congenital Cutaneous Candidiasis: Uncommon Entity or Underdiagnosed?

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Abstract

Purpose of Review We have created a general review of the disease in this article, especially of the clinical features, diagnosis, new treatments and preventive measures.

Summary Congenital cutaneous candidiasis is a vertically transmitted fungal infection which affects term and premature newborn. It is considered as an underdiagnosed pathology, and infection caused by *Candida albicans* is considered the most common aetiology.

Recent Findings Clinically characterized by erythematous papular lesions and pustules with collarette scale. It can also affect other organs and systems by causing an invasive fungal infection. Diagnosis is clinical, and the agent can be isolated; other tools of diagnosis include direct examination and skin biopsy. Regarding the treatment, this infection can be self-limiting in a majority of cases and topical antifungals constitute the treatment of choice. However, in the case of a systemic condition, the first-line treatment is amphotericin B. Prognosis is good, although it is unfavourable in the case of a systemic condition.

Keywords Congenital cutaneous candidiasis · *Candida albicans* · Vulvovaginitis · Vertical transmission · Premature newborn · Antifungal treatment

Introduction

Congenital cutaneous candidiasis (CCC) is a rare condition. However, we suspect that it has a greater prevalence since this condition can often go unnoticed as it has a self-limiting and benign course in most cases. With only under 120 cases reported in the literature, it was first reported in 1960 by Sonnenschein et al. [1].

In most cases, it is triggered by an intrauterine infection through vaginal colonisation by *Candida albicans*, which presents during pregnancy in 20–30% of cases; however, only 1% of individuals develop CCC, which explains the low incidence of the disease [2].

Clinical symptoms occur during the first 6 days of extrauterine life and range from asymptomatic cases and diffuse skin rash to the development of invasive systemic disease which may or may not develop into a skin condition; the latter is associated with high morbidity and mortality. The diagnosis is clinical, but the existence of the fungus in the cultures and the direct examination provide us with accurate diagnosis. It is important to perform tests for differential diagnoses with other skin rashes in the neonatal period to avoid delaying timely treatment and thus avoid complications [3, 4•].

Risk Factors

CCC most frequently occurs in the following cases:

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- In premature infants
- In infants with low birth weight (< 1500 g)
- Mother with *Candida* vulvovaginitis
- Prolonged membrane rupture
- Broad-spectrum antibiotic administration
- Intrauterine foreign body (intrauterine device or cervical cerclage)
- Chorioamnionitis
- Amniocentesis

One of the main defences against *Candida* infection is an intact mucocutaneous barrier, which provides physical and biochemical defence against microorganisms. In premature infants, the epidermal barrier is immature and is compromised, thus predisposing the skin to infection as it allows the penetration of microorganisms into the deeper layers of the skin and their propagation through the bloodstream, which triggers invasive disease. In case of systemic candidiasis development, congenital immunodeficiency should be suspected [4•, 5].

Pathophysiology

The pathogenesis is not well established. According to Sonnenschein et al., CCC occurs due to a combination of maternal vaginal candidiasis, prolonged membrane rupture and prolonged antibiotic administration. CCC is currently known to be secondary to a maternal vaginal infection, which ascends through the membranes, affecting the fetus and leading to a clinical disease; that is, it is a vertically transmitted infection, which appears after birth or during the first days of life. It is important to remember that it can also occur in the prenatal period causing miscarriages and/or foetal death [1, 4•].

Candida spp. colonise the vaginal cavity in pregnant women in up to 30% of cases, where 95% thereof are caused by *Candida albicans* and to a lesser extent by *Candida glabrata.* Besides pregnancy, the presence of intrauterine foreign bodies (intrauterine devices, cervical cerclage) also favours *Candida* colonisation. Its manifestation is asymptomatic in most cases. It is currently known that infection during pregnancy is associated with an increased risk of complications such as the premature rupture of membranes, premature delivery, chorioamnionitis and CCC development [6••].

Candida spp. is known to invade and penetrate intact membranes, generating skin lesions by direct exposure to infected amniotic fluid, while systemic infection occurs by placental invasion and/or the umbilical cord, mostly affecting premature newborn babies or infants with low birth weight [7, 8].

Clinical Manifestations

CCC lesions usually appear shortly after birth from 0 to 6 days. Skin lesions appear on the first day of life in 80% of cases [9••].

The most typical manifestation is a generalised rash comprising small macules, papules and/or pustules on an erythematous base, measuring 5–10 mm, as well as vesicles and/or blisters [Fig. 1]. The most involved topography is the trunk, extensor surfaces, folds and occasionally palms and soles [Fig. 2]; it tends to affect the diaper area and the oral mucosa. In some cases, it can affect nails, generating paronychia and nail dystrophy [10].

Skin lesions usually disappear within 1 or 2 weeks accompanied with peeling, although lesions on palms and soles may persist for a longer duration. Nails tend to go back to normal as they grow [9••, 10].

Premature newborn babies are at a higher risk of developing this systemic condition which may occur with burn-like lesions, as well as indications of respiratory distress, hepatomegaly, hyperglycemia, glycosuria, sepsis or even early neonatal death [9••, 11, 12].

Due to the placental and/or umbilical cord involvement, funisitis may occur, which, upon physical examination, can

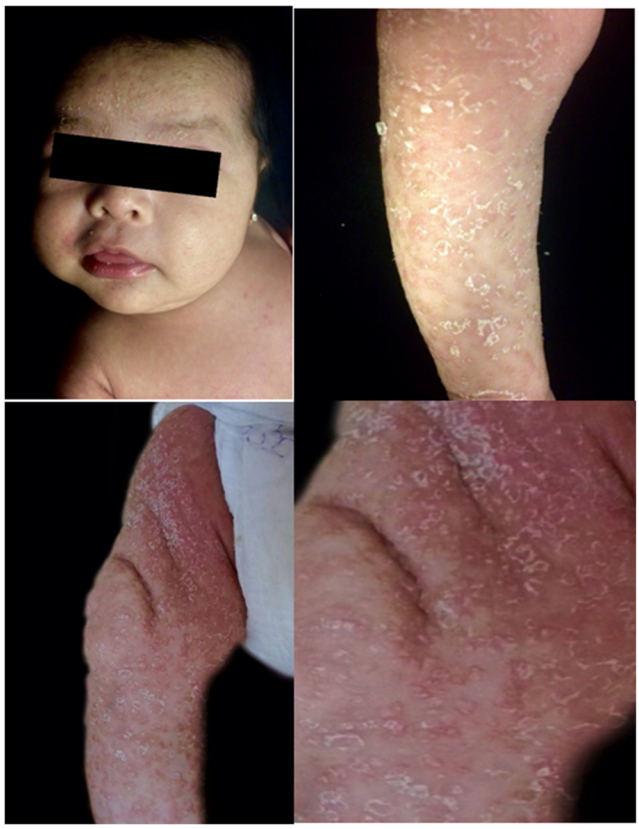

Fig. 1 Papular-erythematous lesions, pustules, with abundant collarette scale, close to the lesions

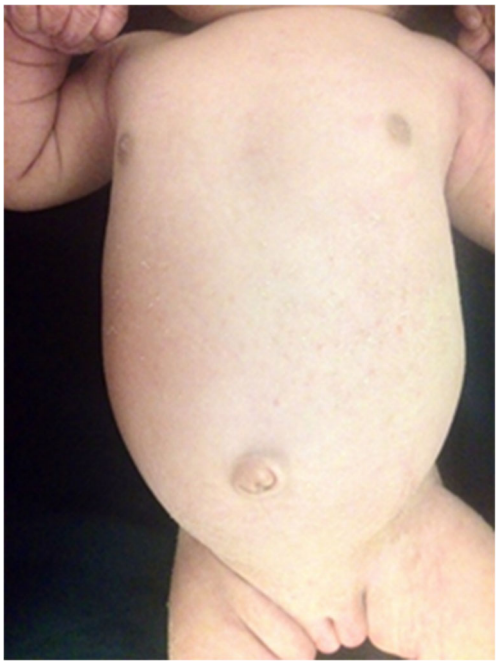

Fig. 2 Most-affected topography

show yellow plaques as well as focal white micro-abscesses from which the microorganism can be isolated [13].

Diagnosis

The diagnosis is clinical; however, it is essential to prove the presence of yeasts and pseudohyphae under direct examination, although only large clusters of yeasts (without pseudohyphae) can be seen in cases of *C. glabrata* infection. The culture is considered the gold standard [Fig. 3]. *Candida* spp. can be identified in the skin through cultures, but obtaining cultures from at least two or more skin rash sites is recommended, as well as obtaining cultures of mucous membranes, placenta and/or umbilical cord to corroborate the diagnosis [9••, 14].

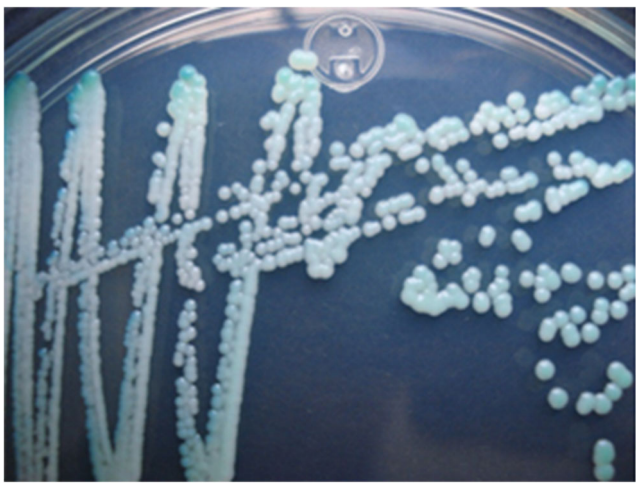

Fig. 3 *Candida albicans* culture

To discard systemic condition, cultures in blood, urine and cerebrospinal fluid (CSF) are recommended, but they are not necessary for the diagnosis.

Skin biopsy with periodic acid–Schiff (PAS) staining or Gromori Grocott shows the presence of yeasts within the stratum corneum, either with the presence of pseudohyphae plus blastoconidia or only the latter [8].

In addition, obtaining maternal cultures from the vagina, placenta or amniotic fluid can help us recognise the infection in early stages [6].

It is important to discard other diagnoses during the neonatal period which present dermatosis with similar characteristics (Table 1).

The early identification of the disease avoids unnecessary tests and excessive treatment of symptomatic newborn babies.

Treatment

Typically, the course of the disease is benign in term newborn babies and they will usually require only topical antifungal treatment, which is considered the first-line treatment, and the use of imidazole is preferred because of its action against *Candida* spp. The main antifungals are bifonazole, clotrimazole, miconazole, isoconazole and especially sertaconazole. However, there are no clinical trials that determine the optimal duration of treatment, and topical antifungal treatment must be provided until the lesions resolve [15].

Systemic antifungal therapy is reserved for patients with risk factors such as respiratory distress data, early sepsis, leukocytosis, bandemia, hyperglycemia and persistent glycosuria, among others. As well as in newborns presenting burn-like dermatosis or with positive blood, or urine or CSF cultures for *Candida spp*. In general, *C. albicans* is susceptible to most antifungals; however, *C. glabrata* has developed resistance to fluconazole. Another criterion for initiating systemic treatment is the history of instrumental delivery, invasive procedures, immunodeficiencies associated with an increased risk of systemic dissemination and, therefore, a poor prognosis [9••, 10–15].

Amphotericin B deoxycholate is the first-line antifungal for systemic treatment, at dosages of 0.5–1 mg/kg/day. Although, amphotericin B is the treatment of choice, adverse effects that include nephrotoxicity, hepatotoxicity and bone marrow suppression are its main disadvantage. The presentation of liposomal amphotericin B (3–5 mg/kg/day) is preferred in patients with severe kidney failure, since fewer side effects have been reported. Most treatment guidelines recommend the use of this type of amphotericin B. 5-Flucytosine, at dosages of 50–100 mg/kg/day, is used in combination with amphotericin B for

Table 1 CCC differential diagnoses

Diagnosis	Age of appearance	Clinical manifestations	Affected area	Findings
Impetigo	First weeks of life	Pustules, blisters, occasional vesicles	Mainly in the diaper area, periumbilical	- More frequent by colonisation of *S. aureus* on the skin - Gram staining: cocci PMN gram-positive in groups - Cultures of bacteria
Neonatal candidiasis	Days to weeks of life	Erythematous-scaly molecules with pustules and satellite lesions	Diaper area and other intertriginous areas	- Generally, it affects healthy NB - If pustules, KOH: hyphae, budding yeasts
HSV infections	It occurs from birth or 5–14 days of life; by active maternal infection and/or acquired primary infection during pregnancy	Vesicles, pustules, scabs, erosions, scars, sepsis signs	Any area; especially scalp, trunk; mucous membranes or any skin site	- They are low birth weight NB with microcephaly, chorioretinitis - Tzanck, PCR, virus cultures
Toxic erythema of the newborn	Usually 24–48 h, after birth or at 2 weeks of life	Erythematous macules, papules, pustules	Any site except palms and plants	- They are term NB > 2500 g - Clinical; Wright's stain: eosinophils
Pustular melanosis of the newborn	At birth	Pustules without erythema; collarette scale; hyperpigmented macules	Anywhere; more frequently in forehead, ears, back, hands, and feet	- Clinical; Wright's stain: PMN, occasional eosinophils and cellular debris
Benign cephalic pustulosis	Days to weeks	Papules and pustules on an erythematous base	Cheeks, forehead, neck, trunk, scalp	They are healthy NB and it is due to colonisation of *Malassezia* spp.
Miliary	At birth or little after death	Papules, fragile vesicles with or without erythema	Forehead, upper trunk, arms	- There may be a history of overheating or fever - The diagnosis is clinical
Congenital syphilis	At birth or during the first days	Blisters or erosions	Especially in hands, feet and periorificial	- By transplacental intrusion of *Treponema pallidum* - Dark-field exam; serologies for syphilis, skin biopsy - Hematogenous spread, affecting the skin, liver, bones, mucous membranes and CNS

PMN polymorphonuclear, *KOH* potassium hydroxide, *HSV* herpes simplex virus, *CNS* central nervous system, *NB* newborn

CNS infection; however, this drug is largely inaccessible in various countries [15].

Echinocandins (caspofungin or micafungin) are also indicated in the treatment. Caspofungin is well tolerated, without significant adverse effects, but, for now, its use is contraindicated when the CNS is compromised, due to the lack of conclusive studies that assess the efficacy of treatment in this age group [16•].

Micafungin has similar efficacy and safety as amphotericin B liposomal in paediatric patients (including neonates). The recommended doses in neonates range from 2 to 4 mg/kg up to 10 mg/kg. Increasing the dosage in up to 15 mg/kg is recommended in CNS infections, thereby achieving fungicidal concentrations in the CSF with an adequate safety profile [17].

Another alternative is fluconazole at dosages of 6–12 mg/kg/day, which can be used in cases of resistance or toxicity by amphotericin B, and it is the only one that crosses the CNS. The administration time of the systemic therapy is 14 days (average 7–28 days). Delay in treatment, the use of oral or topical nystatin and treatments < 10-day duration are associated with a greater hematogenous dissemination which enhances complications. Therefore, the early identification of this pathology is crucial to initiate an empirical treatment that prevents its dissemination at a systemic level [18, 19].

The early treatment is the most important factor associated with survival in systemic infections.

Dissemination in blood, urine or CSF can occur in approximately 60% of newborn babies weighing < 1000 g compared to 33% in those weighing 1000–2500 g, and 11% in newborn babies weighing > 2500 g. Mortality occurs in 40%, 15% and 4%, respectively; therefore, cultures must be obtained of both skin, blood and CSF in these cases to avoid delay in starting the treatment. Empirical therapy should be initiated immediately even when cultures are pending results and especially in patients who already have the aforementioned risk factors [20].

Management during pregnancy can also be useful, as it helps prevent CCC. While it is not a universal practice, pregnant women should be examined for vaginal candidiasis, especially in the third trimester. Vulvovaginitis management during pregnancy is based on topical intra-vaginal imidazole for 7 days [21].

Prognosis

The prognosis of this entity also depends on the patient's general condition. In normal weight term newborn babies, without perinatal complications or comorbidities, the prognosis is excellent. Patients with risk factors such as prematurity, low weight, invasive procedures due to other comorbidities or immunocompromised can have a bad or fatal prognosis because of the high risk of disease dissemination [8]. Especially, premature babies of extremely low birth weight (< 1000 g) are at a higher risk of presenting scaly or erosive forms similar to burns, greater risk of invasive fungal infection and early neonatal death than those weighing > 1000 g [9••].

Conclusions

In addition to the aforementioned factors, no other predisposing factor (maternal or foetal) has been confirmed for the appearance of CCC; therefore, the discrepancy between the frequency of the recognised predisposing conditions and the number of reported cases is striking, a reason why we should investigate the existence of other factors determining its appearance. On the contrary, CCC is more frequent than what is generally thought and, due to its favourable progress, in many cases, it goes unnoticed or is confused with other dermatoses appearing in the neonatal period. This is due to the lack of familiarity of first contact practitioners, as well as primary care practitioners, gynaecologists, paediatricians and neonatologists with this entity.

We believe that familiarisation with this pathology is necessary and that it is important for doctors to become involved in the care of the mother–baby binomial during the perinatal period in order to make a timely diagnosis, thus preventing potential complications in infants with risk factors for systemic infection. The proper communication and collaboration between the different specialties is equally invaluable for an early diagnosis.

We believe that if this form of candidiasis were diagnosed more frequently, a better estimate of its true prevalence could be achieved, and other predisposing factors that could potentially have an impact on preventing the disease and on its complications could also be detected, if the cases were carefully analysed.

Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SPAP and TBME. The first draft of the manuscript was written by SPAP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest Alicia Sanchez-Padilla, Adriana Valencia-Herrera, Mirna Toledo-Bahena, Carlos Mena-Cedillos, Mario Duarte-Abdala, Marcela Salazar-Garcia and Alexandro Bonifaz declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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