

# Usefulness of the Acute Phase Reactants (APR) Score [part 5]: Subcutaneous Abscess Due to *Candida Albicans* in a Preterm Infant

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## ABSTRACT

Subcutaneous abscesses in neonates are mainly caused by local infections with indwelling intravascular catheters. *Candida albicans* is a pathogen that is rarely associated with subcutaneous abscesses. In the present case, the patient was delivered vaginally after premature rupture of membranes for 3 weeks. The patient was a female infant with a gestational age of 32 weeks and 3 days and a birth weight of 1792 g. At 11 days of age, she experienced frequent sudden apnea attacks. A blood test revealed a mild inflammatory reaction, and sepsis was suspected. After blood culture, the administration of antibiotics was started immediately. At 14 days of age, a red lesion of approximately 1.5 cm in diameter was observed on the patient's left shoulder. Two hours later, a mass with heat appeared at the same site. Treatment was started under the diagnosis of bacterial infection. The clinical course was characterized by a particularly poor decline in alpha 1-acid glycoprotein until the use of antifungal drugs. The present case underscores the usefulness of applying the acute phase reactant score (APR score) in parallel with clinical symptoms. After that, because the symptoms did not improve, a test puncture was attempted at 18 days of age. Since *Candida albicans* was isolated and identified, antibiotics were changed to antifungal agents from 19 days of age. As a result, the patient's APR score decreased, and her symptoms improved. There was no recurrence and there were no signs of immunodeficiency after the discontinuation of antifungal therapy. When a neonatal subcutaneous abscess does not improve as expected with the administration of antibiotics, it is important to consider the possibility of a fungal infection and to actively perform experimental puncture in order to identify the pathogen.

**Keywords:** Acute Phase Reactant Score (APR Score); *Candida Albicans*; Subcutaneous Abscess; Preterm Infant; Hematogenous

## Introduction

*Candida albicans* in neonates is known to cause various infections ranging from superficial dermatitis to systemic candidiasis. In particular, *Candida albicans* is known to cause superficial dermatitis, typified by diaper dermatitis. Cases involving subcutaneous abscess formation are extremely rare (William E, et al. [1]). Although there are sporadic reports of infant and adult cases, our review of the relevant literature yielded only two cases with a neonatal onset (O J Hensey, et al. [2]). We report the case of a premature infant with a skin abscess caused by *Candida albicans*. Informed consent for the publication of

this report was obtained from the parents, and this fact was documented in the patient's medical record.

## Case

Eleven-day-old female infant.

## Chief Complaint

Frequent apnea attacks.

## Maternal Information

The mother (gravida, 3; parity, 1) had premature rupture of mem-

branes at 29 weeks of gestation and was transferred to our emergency maternal hospital for management purposes.

**Course before the Disease Onset**

After admission to our hospital, the administration of magnesium sulfate, sulbactam sodium/ampicillin sodium to the mother was started. Antibiotics were discontinued after 10 days because a vaginal culture on admission was negative and the inflammatory reaction was not enhanced. As a result, the membranes completely ruptured at 31 weeks and 6 days of gestation. At 32 weeks and 3 days of gestation, she went into labor and gave birth to a girl by vaginal delivery. The infant had a birth weight of 1794 g and an Apgar score of 8 at both 1 minute and 5 minutes. Grunting was observed shortly after birth, but a gastric juice microbubble test was strong, chest X-ray findings revealed transient tachypnea in the newborn, and respiratory management was started with nasal continuous positive airway pressure (CPAP). After confirming that APR score remained at 0 until 2 days of age and that blood cultures on her admission were negative, treatment of empiric antibiotics was terminated. On day 9, she was transferred to total enteral feeding and planned removal of the PI catheter that had been in place since admission was performed.

**Course after the Disease Onset (Table 1)**

At 11 days of age (corrected 34 weeks 0 days), the patient experienced frequent sudden apnea attacks. Blood samples were immedi-

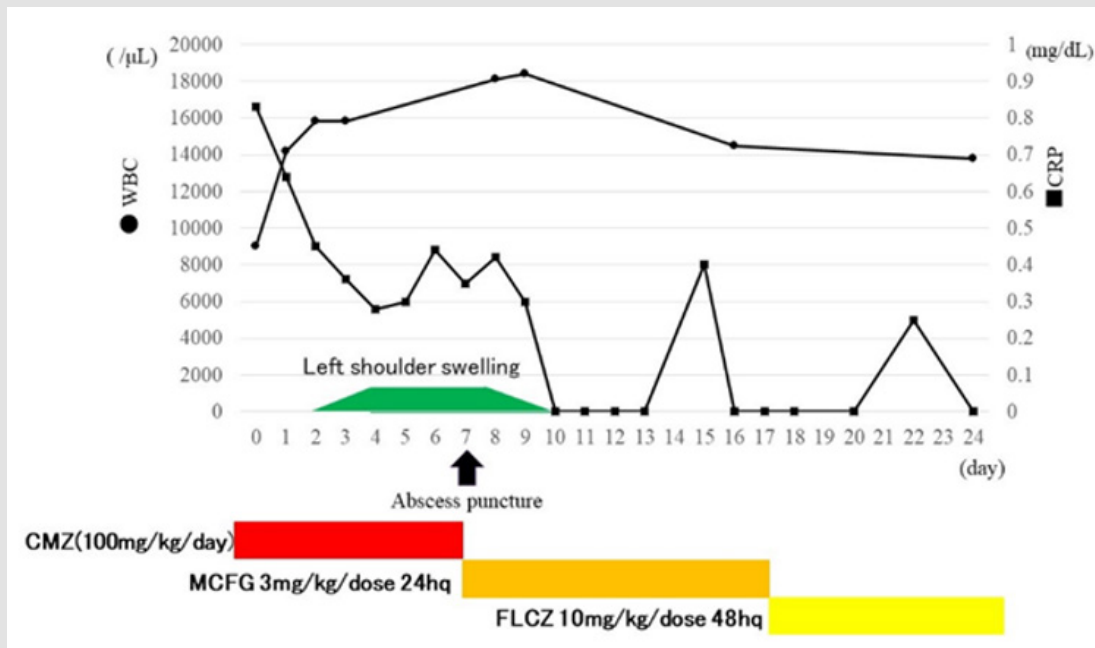
ately collected. The results showed an increase in CRP and alpha1-acid glycoprotein ( $\alpha$ 1-AGP). Cefmetazole sodium (CMZ 200 mg/kg/day) was initiated under a diagnosis of clinical sepsis. On day 13, erythema and erosion on the buttocks, presumed to be *Candida* dermatitis, were observed, and ketoconazole was applied to the same site.

**Table 1:** Blood examination on the day of onset.

With Blood Cells	9,000/ $\mu$ L		Blood Gas Analysis	
Differential	Segments	22%	pH	7.448
	Eosinophils	8%	PCO <sub>2</sub>	41.5 mmHg
	Lymphocytes	59%	HCO <sub>3</sub> <sup>-</sup>	28.7 mEq/L
	Monocytes	10%	Base Excess	4.2 mEq/L
	Atypical Lym	1%		
Red Blood Cells	3.89 $\times$ 10 <sup>6</sup> / $\mu$ L		Acute Phase Reactants	
Hemoglobin	13.8 g/dL		CRP	0.83 mg/dL
Platelets	14.2 $\times$ 10 <sup>3</sup> / $\mu$ L		AGP	105 mg/dL
			Hp	<20 mg/dL
			APR score	2 Points

**Symptoms at Onset (11 days of age)**

Body weight 1666 g, body temperature 37.1°C, heart rate 150 beats/min, respiratory rate 46 beats/min, no swelling of the great fontanel, no abnormalities of the chest or abdomen, no abnormalities of the skin, and normal muscle tone.



**Figure 1:** Clinical course of inflammatory data and treatment. After receiving the test puncture and culture results, antifungal drugs were started, and the local findings improved. Antifungal drugs (MDFG and FLCZ) were administered for a total of 16 days.

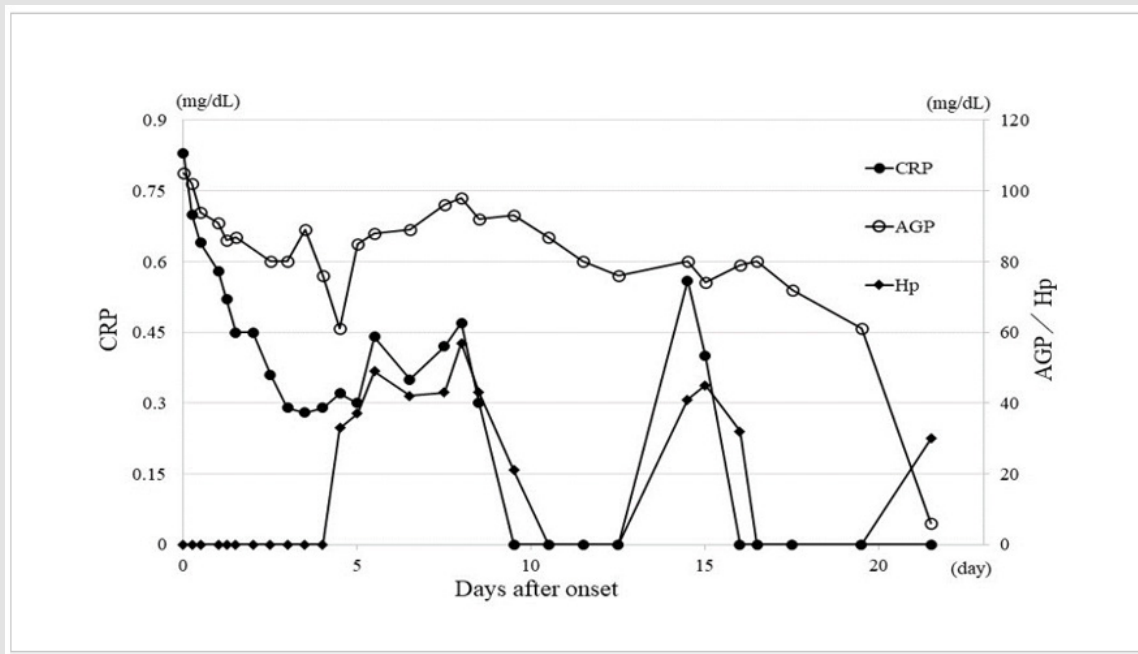


Figure 2: Serial changes of APRs after the onset



Figure 3: Left shoulder skin findings  
 The left photograph shows an image of the left shoulder just before the puncture at 18 days after birth. The right photograph shows crusting after the puncture at 20 days after birth. A red lesion of 1.5 cm in diameter was observed on the left shoulder, and swelling was also observed over the next day. After puncture, pigmentation remained, and the area shrank.

**Treatment Course**

The treatment course is shown in (Figures 1-3). Blood cultures taken at 11 days of age (day 0 of illness) and 14 days of age (day 3 of illness) were negative, but infection was confirmed. Since it could not be completely ruled out, the dose of CMZ was reduced from 200 mg/

kg/day (the dose for sepsis) to 100 mg/kg/day, and administration was continued. The inflammatory response gradually improved (Figure 1). However, on the same day, a red lesion of 1.5 cm in diameter was observed on the patient’s left shoulder, and two hours later, an elastic-hard mass with a feeling of heat and mobility appeared (Figure 3). The erosion of the buttocks tended to improve. CRP and α1-AGP

stopped trending down from day 15 (day 4 of illness) (Figure 2). Local findings, such as redness and swelling of the left shoulder, showed little improvement, so a test puncture was performed on the same site at 18 days of age (day 7 of illness). As a result, whitish-yellow pus was aspirated. MRI was performed at 19 days of age, and it was confirmed that the inflammation had not spread to the bone marrow. Since *Candida albicans* was detected in the puncture culture at 18 days of age (day 7 of illness), it was determined to be the causative bacterium. After switching to MCFG, the inflammatory reaction decreased, and local findings such as swelling around the shoulder joint improved (Figure 1). In response to the results of susceptibility testing at 28 days of age (day 17 of illness), fluconazole (FLCZ) was changed to 10 mg/kg/dose every 48 hours, taking into consideration the Japanese candidiasis treatment guidelines.

Antifungal drugs were administered for a total of 16 days (Figure 1). Thereafter, no recurrence of symptoms was observed, and an ophthalmologic examination and brain MRI revealed no abnormal findings. After discharge, the patient was followed as an outpatient, but there were no episodes of immunocompromise, and the patient recovered without scarring at the site of abscess formation or pigmentation.

## Discussion

*Candida albicans* is an indigenous bacterium of the gastrointestinal tract and genital mucosa. In the neonatal period, engraftment of the bacterium is observed in 50% of individuals at 1 week and 75% at 1 month. Risk factors for *Candida* infection in newborns after 1 week of age, such as the present case, include vaginal delivery, extremely premature infant, very low birth weight infant, long-term administration of antibiotics, and placement of central venous catheters (Mori M [3]). The risk factor in the present case was vaginal delivery. However, *Candida albicans* was not detected from the vaginal culture at maternal admission. It is known that as pregnancy progresses, estrogen increases, and the properties of vaginal cultures change, increasing the detection rate of *Candida albicans* (Mizuno S [4]). Even though *Candida albicans* was not identified after the examination performed on admission, the possibility that the infant was exposed to the bacterium via the maternal vaginal route at birth, approximately 3 weeks later, cannot be ruled out. Subcutaneous abscesses in neonates are primarily caused by local infection due to the use of intravascular central catheters. The typical causative bacteria are *Staphylococcus aureus* and *Staphylococcus epidermidis*, subcutaneous abscesses caused by *Candida albicans*—as observed in the present case—are rare, with only two cases reported in the relevant literature (O J Hensey, et al. [2]).

In one of the cases, an intravascular catheter was not placed. In this case, the central venous catheter had already been removed 2 days before the onset of apnea (i.e., 5 days before the formation of the subcutaneous abscess). There was no abrasion at the site where

the subcutaneous abscess was formed, and it was not a local infection caused by direct infiltration from the surface. It is hypothesized that *Candida albicans* may enter the bloodstream via devices such as intravascular catheters and hematogenous infection through direct infiltration from the intestinal mucosa (LD Pappu Katikaneni, et al. [5]). *Candida albicans* is transported to each organ through the blood stream, settles around the capillaries, and begins to proliferate. Intestinal and oral *Candida* migrate into the blood, causing deep candidiasis (Kamikawa K [6]). Therefore, the detection of fungi should be performed at multiple sites and the presence of *Candida*-like dermatitis should be monitored for progression to deep-seated candidiasis, including candidemia (Mori M [3]). Since the infant also had diaper dermatitis, which was thought to be associated with *Candida*, it was considered possible that hematogenous abscess formation had occurred from the intestinal tract. In the present case, no significant bacteria were detected in the blood culture at the onset. The sensitivity of adult blood cultures in the detection of *Candida albicans* is only 50%, and because the volume of blood used in neonatal and infant cultures is smaller than that in adults, the detection rate for *Candida* species in such blood cultures is even lower (Rachel G, et al. [7]).

Therefore, systemic *Candida* infection cannot be ruled out simply because the blood culture was negative for *Candida*. In addition, in this case, an increase in blood  $\beta$ -D glucan was observed (279 pg/mL).  $\beta$ -D glucan alone is useful in the diagnosis of candidemia, and it has been reported that candidemia is highly likely to occur if the concentration of  $\beta$ -D glucan is  $\geq 13.86$  pg/mL (Guo J, et al. [8]). According to the same report, among *Candida* spp. *Candida albicans* is associated with a large increase in  $\beta$ -D glucan. Furthermore, the possibility is considered to increase when CRP is weakly positive (0.06–0.61 mg/dL). The infant's  $\beta$ -D glucan and CRP levels also seem to suggest this. *Candida* infection is often treated with FLCZ or MCFG. The optimal amount of MCFG needs to be examined in the future. FLCZ is most commonly used in neonates and is associated with a higher degree of safety (Oishi M [9]). Although good progress was observed during treatment with MCFG, we attempted to change to FLCZ during the course of treatment. In this case, the inflammatory response did not improve during treatment with antibiotics, and it was difficult to identify a causative bacterium. A definitive diagnosis of fungal infection requires fungal detection from aseptically-collected specimens. Although most subcutaneous abscesses are caused by bacteria, the physician should not hesitate in performing puncture if the local symptoms do not improve with antibiotic treatment.

## Conclusion

Most neonatal subcutaneous abscesses are caused by bacteria, but fungal causes are also possible. If a prolonged increase in the inflammatory response is observed during treatment with antibiotics, the active performance of abscess puncture (after confirming its safety) is necessary to identify the causative pathogen, including fungi.

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