Saccharomyces cerevisiae Sepsis Following Probiotic Therapy in an Infant

A 3.5-month-old infant with undiagnosed underlying combined immunodeficiency presented with *S. ceravisiae* fungemia following treatment with *S. boulardii* containing probiotic preparation. This case highlights that the use of probiotics in sick patients may be fraught with danger.

Keywords: *Adverse effects*, *Immunodeficiency, Invasive fungemia, Probiotics*.

Saccharomyces boulardii, a non-pathogenic yeast very commonly used in the bakery industry, is also used as probiotic therapy in a variety of conditions. Its use has been increasing rapidly, even in very small children [1]. Probiotic treatment with *S. boulardii* is reported to cause invasive fungemia by the related subtype *S. cerevisiae*. This is found particularly in premature infants and those with underlying immunocompromised state or with chronic debilitating conditions.

A 3½-month-old male infant was admitted with history of watery diarrhea for three days. The child had three episodes of respiratory tract infection since one month of age, which had been treated with oral antibiotics. In order to prevent antibiotic-associated diarrhea, the baby had also been prescribed probiotic preparation containing *S.boulardii* 250 mg twice daily for the 10 days during each episodes. The baby was born at term gestation by Cesarean section and his birth weight was 2.7 kg. He was the first baby born to non-consanguineous parents. His weight on admission was 3.9 kg (<3rd percentile). For unspecified reasons, the baby had not received any vaccines since birth. During the current admission, the child was malnourished and dehydrated. He had intermittent fever (up to 102°F), and erythematous macular skin rashes over the trunk and limbs. The liver was enlarged, there was no splenomegaly. There were few discrete palpable lymph nodes in the cervical region (<1 cm). Blood investigations revealed hemoglobulin of 11.4 g/dL and total WBC count of 3400 with 74% neutrophils. The C-reactive protein was mildly raised; liver and renal function tests were normal. Malarial parasite and dengue antigen tests were negative. The urine culture was sterile. Chest *X*-ray revealed prominent bronchovascular markings on either side, with a barely discernible thymic shadow. The blood culture grew the fungus *S.cerevisiae*, sensitive to Amphotericin B and Caspofungin. The parents shifted the baby to another hospital for financial reason where he was treated with a two week course of intravenous Amphotericin B. Immunological work-up performed during this period revealed combined T and B cell deficiency (***Table* I**). The parents declined any further genetic tests, and got the infant discharged against medical advice. They did not come for follow-up.

Invasive fungal sepsis by the normally non-pathogenic strains of *S. cerevisiae* following therapy with *S. boulardii* is being reported increasingly. *S. boulardii* strains are asporogenous strains of *S. cerevisiae*, and hence should not be regarded as a different species [2].

S. cerevesiae is responsible for 0.1-3.6% of all fungemia; the incidence having been on the rise since the introduction of *S. boulardii* as probiotic in 1991 [3]. Most cases of *S. cerevisiae* fungemia, have been described in infants [4]. All such infants have underlying conditions such as prematurity, acute leukemia, congenital malformations, burns, abdominal surgery, severe neutropenia or permanent central venous catheters [1,5].

S. boulardii in a dose of 250-750 mg/day typically for 5-7 days is recommended treatment in addition to rehydration therapy in acute gastroenteritis has been shown to be effective in prevention of antibiotic-

TABLE I IMMUNOLOGICAL TESTS FOR T CELL AND B CELL FUNCTION IN THE PATIENT WITH *S. CEREVISIAE* SEPSIS

Test description	*Observed value*	*Biological reference range*
*CD45 absolute	720	1000-3000
#CD3: absolute	324	1900-5900
percentage	45%	49-76
#CD4: absolute	137	1400-4300
percentage	19%	31-56
CD8: absolute	173	500-1700
percentage	24%	12-24
CD4/CD8 Ratio	0.79	≥1.0
Serum IgG total, mg/dL	226	350-1620
Serum IgA total, mg/dL	0.52	1-91
Serum IgM total, mg/dL	<10	30-183

associated diarrhea [6]. The safety profile of probiotic preparations are generally considered satisfactory but caution must be exercised when prescribing them to patients with suspected compromise of the immune status. If underlying immunodeficiency is missed or overlooked, this seemingly harmless medication may have devastating consequences.

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Life-threatening Hypercalcemia as the First Manifestation of Acute Lymphoblastic Leukemia

Hypercalcemia of malignancy, usually reported in adults in advanced stages, is rare in children. A 4-year-old boy presented with intermittent episodes of severe hypercalcemia, which improved with intravenous hydration therapy, furosemide and bisphosphonates as the initial manifestation of occult acute lymphoblastic leukemia. Pediatricians should rule out hematological malignancy in patients with severe hypercalcemia.

Keywords: *Constipation, Diabetes insipidus*.

Severe hypercalcemia (>14 mg/dL) is rare in children but can result in coma, arrhythmias and death. In adults, the most common cause of severe hypercalcemia is malignancy (advanced stages), which portends a poor prognosis. Hypercalcemia of malignancy has been rarely reported in children [1]. We present a boy with life-threatening hypercalcemia who was diagnosed with occult acute lymphoblastic leukemia (ALL).

A 4-year-old boy presented with recurrent vomiting, polyuria, polydipsia, extreme irritability, irrelevant talk, constipation and right leg immobility with the history of low back pain for two months. The child was in severe dehydration with altered sensorium, high blood pressure (>99th centile) without any neurological deficit, hepatosplenomegaly or lymphadenopathy. On laboratory investigations, serum calcium was 19.2 mg/dL (ionized 8.2 mg/dL), phosphate 3.7 mg/dL, albumin 3.7 g/dL, alkaline phosphatase 389 IU/L, high urinary calcium: creatinine ratio, 25(OH)D 40 nmol/L (normal 50-250), increased 1,25$(OH)_2$D 271 pmol/L (normal 52-117); and normal venous blood gas, renal function and serum magnesium. He was managed with hydration with double maintenance fluid and intravenous furosemide. Pamidronate (1 mg/kg) was administered over 4 hours by intravenous infusion. The serum calcium improved to 9.2 mg/dL and subsequently fell to 6.8 mg/dL over the next 3 days requiring oral calcium supplementation. A diagnosis of primary hyperparathyroidism was considered based on serum PTH level of 106 pg/ml (15-68.3) and doubtful PTH gland adenoma on ultrasound of neck. Sestamibi scan, 4D CT neck and 4D MRI neck did not identify any parathyroid gland abnormality. A repeat serum PTH was reported low at 1.3 pg/mL with normal calcitonin (<2 pg/mL, normal 0-18.2). Work up for PTH-independent causes of hypercalcemia including granulomatous disease (tuberculosis and angiotensin-converting enzyme levels for sarcoidosis) was normal.

Radiographs showed extensive generalized bony lytic lesions of skull (salt and pepper appearance), phalanges