Pulmonary candidiasis treated with 5-fluorocytosine

Infection with Candida albicans occurs only when there is impaired host defence, such as in debilitating disease, after prolonged treatment with antibiotics or central venous catheters (Goldstein and Hoeprich, 1972), in immunological deficiencies (Kirkpatrick, Rich, and Bennett, 1971), or after treatment with prednisone and immunosuppressives (Folb and Trounce, 1970). 4 patients with pulmonary candidiasis without such predisposing factors, one of whom died, have been reported (Arthur, 1969; Stevens, Jameson, and Philpott, 1972). We report the development of severe pulmonary infection in a previously healthy girl who was cured with 5-fluorocytosine (Isacson et al., 1972).

Case report

A 10-year-old girl was admitted to hospital on 11 January 1972 because of tonsillitis and pneumonia. She had previously been in good health. At the age of 6 she had been vaccinated with BCG and subsequently became tuberculin positive. In December 1971, she had rhinitis and cough for a few days. On 5 January 1972 she developed a fever and a sore throat. 3 days later her physician took a throat swab which was positive for Candida albicans, gave two injections of penicillin, and referred her to hospital.

On admission the girl was acutely ill and dyspnoeic. She had conjunctivitis, rhinitis, and pharyngitis. The tonsils were covered with thick white membranes, a Gram-stained preparation of which showed abundant fungal hyphae, cultures being positive for C. albicans. Cervical lymph nodes were massively enlarged. An initial chest x-ray showed enlarged hilar nodes and bilateral hilar infiltrations. No pathogen was detected except for massive growth of C. albicans from throat, sputum, and stools. The sedimentation rate was 25 mm in the first hour. Leucocytes were 9100/mm² with 47% band forms. Peripheral lymphocytes and bone marrow studies were unremarkable.

During the next days, dyspnoea worsened in spite of administration of several broad-spectrum antibiotics. Fever up to 40 °C, severe respiratory distress, cyanosis, and lung enlargement developed. The chest x-ray (Figs.) suggested miliary tuberculosis. Para-amino-salicylic acid and isoniazid were given with no improvement.

During this critical stage, C. albicans was also cultured from urine. Nystatin (1,000,000 units/day orally) did not suppress the growth of C. albicans.

Ten days after admission, treatment with 100 mg 5-fluorocytosine/kg body weight/day was successful for a total of 6 weeks. Because of diarrhoea and high serum transaminase levels the dosage was not increased. After 2 weeks of this treatment, fever and dyspnoea disappeared. A 3-week course of prednisone (1 mg/kg body weight per day) was started. On March 29, 10 weeks after admission, the girl had recovered and was discharged. Chest x-rays still showed large hilar nodes and minor interstitial changes of the lungs. C. albicans continued to be grown from the throat and stools after recovery, but hyphae were no longer visible and the fungus had become resistant to 5-fluorocytosine in vitro.

The girl was followed-up for one year, during which time she regained excellent health and showed normalization of chest x-rays and pulmonary function tests.

Immunological observations. Granulocyte function was assessed by the nitro blue tetrazolium test (Rubinstein and Pelet, 1973). 7% of cells spontaneously reduced the dye (normal values 0–4%), and 96% did so after stimulation with bacterial antigens (normal values 84–100%). These results indicate normally functioning granulocytes which react to infection.

The serum IgM level was raised initially to 1000 mg/100 ml (normal values 38–135). Blood levels of IgA and IgG, IgA secreted in tears and saliva, and electrophoretic and immuno-electrophoretic patterns of serum proteins were all normal. There were positive titres of complement fixing antibodies against influenza and parainfluenza virus, adenovirus, and mycoplasma, of haemagglutinating antibodies against influenza virus, and of isoaagglutinins anti-A1 and anti-A2. No antibodies were detectable against toxoplasmosis, ornithosis, herpes, Q fever, brucellosis, or C. albicans. These titres did not rise during the disease. Titres of haemagglutinating antibodies against C. albicans (Müller, 1972) stayed negative until 28 April and subsequently rose to 1:20.

Skin tests with C. albicans antigen (Candidin, Institut Pasteur, Paris) and Tuberculin Purified Protein Derivative (Serum- and Impf Institut, Berne) were negative during the acute phase of the disease, but

Supplied as 'Ro 2-9915' tablets by Hoffmann-La Roche, Basle, Switzerland.

converted to positive one month after recovery. At that time skin tests with mumps antigen and streptodornase were positive, as they were to dinitrochlorobenzene after sensitization. Lymphocyte function was assessed by the phytohaemagglutinin stimulation test and by the mixed lymphocyte culture test. (Skin tests and lymphocyte function tests were done according to Fudenberg et al., 1971.) The results of these tests are presented in the Table. Reaction of the lymphocytes to phytohaemagglutinin was expressed as the Stimulation Index which is the disintegrations per minute (dpm) of incorporated radioactive thymidine of stimulated cells/dpm of incorporated radioactive thymidine of non-stimulated cells. Results of the mixed lymphocyte

TABLE
Some immunological data in a case of pulmonary candidiasis

<table>
<thead>
<tr>
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<th>20 Jan 72</th>
<th>11 Feb 72</th>
<th>28 April 72</th>
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<td>Candidine 1/1000</td>
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<td>Tuberculin 1/1000</td>
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<td>Phytohaemagglutinin stimulation index of lymphocytes*</td>
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<td>Mixed lymphocyte culture* (disintegrations/min)</td>
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<td>142</td>
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</table>

*Details in text.
†Lymphocytes killed with mitomycin.
culture are given as dpm of total incorporated radioactive thymidine. In the initial phase of the disease, before prednisone therapy began, lymphocytes showed depressed responses to phytohaemagglutinin and in the mixed lymphocyte culture. Both tests were normal during the period of recovery in hospital and remained so thereafter.

Discussion

This patient developed pulmonary candidiasis in the absence of common predisposing factors. Her immune system, however, was temporarily compromised. The cellular system was functionally deficient during the initial phase of the disease, as shown in vivo by negative responses to skin tests with candidine and tuberculin, and in vitro by abnormal stimulation of lymphocytes with phytohaemagglutinin and in the mixed lymphocyte culture. All these reactions returned to normal with clinical recovery. The humoral immune system was also transitorily abnormal, as shown by the lack of rise of C. albicans haemagglutinating antibodies for 10 months, with a subsequent rise to titres of 1:20. Such a specific lack of antibody formation against C. albicans in systemic candidiasis has not been observed before (Müller, 1972).

We suggest that the preceding respiratory infection, which was probably viral in nature, was responsible for the transitory cellular immune deficiency, since depression of cellular immunity is known to occur in several viral infections (Wheelock, Toy, and Stjernholm, 1971). The humoral deficiency occurred either independently or was secondry to the cellular defect as discussed by Mitchell, Mishell, and Herzenberg (1971).

The successful treatment of this life-threatening fungal pneumonia with 5-fluorocytosine is noteworthy.

Summary

Severe pulmonary infection with C. albicans developed in a previously healthy girl, in the absence of any condition known to predispose to fungal infection. In a critical stage of the illness she was treated with 5-fluorocytosine (100 mg/kg per day orally), and thereafter recovered completely.

Immunological studies showed that the patient’s cellular and humoral immune systems were transitorily depressed. A viral infection preceding the mycotic invasion was a possible cause of the temporary immune deficiency.

References


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The low birthweight African baby

About 10 years ago Gruenwald (1963) clearly differentiated two types of low birthweight babies—those whose birthweight was low because of true prematurity, and those who had suffered intrauterine growth retardation and were consequently small for gestational age. This concept has since been elaborated upon by many workers (Battaglia and Lubchenco, 1967; Yerushalmy, 1967; Ounsted, 1968) and forms the basis for all modern studies on this subject. The incidence of the two groups is well established in advanced socioeconomic communities (Butler and Bonham, 1963; Gruenwald, 1966), but no evaluation has been carried out in an underprivileged African community.

The following is a survey of the relative incidence of the two types of low birthweight babies in an African subeconomic community and an assessment of the significance of known aetiological factors in these cases.

Materials and methods

Baragwanath Hospital serves an African population exclusively; of 18,000 newborns annually, 3500 (19.5%) weigh less than 2.5 kg. This has necessitated the