

DEFICIENT NEUTROPHIL FUNCTION IN A PATIENT WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS, THYMOMA AND MYASTHENIA GRAVIS

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Abstract. The case of a 68-year-old man who suffered the onset of chronic mucocutaneous candidiasis, thymoma, myasthenia gravis and a reversible neutrophil dysfunction during adult life is reported. All tests for humoral and cellular immunity proved normal. Thymectomy and the administration of transfer factor had no effect on the skin disease. Long-term oral administration of 5-fluorocytosine almost cleared the skin lesions; the neutrophil defect disappeared.

Key words: Chronic mucocutaneous candidiasis; Thymoma; Myasthenia gravis; Granulocytes; Microbicidal tests

Chronic mucocutaneous candidiasis (CMC) with onset during the early years of life is an infrequent disease (34). Immunological deficiencies are currently considered as being implicated in the pathogenesis and several clinico-genetic entities appear to exist (33, 34). CMC with onset in adult age is rare, however. 8 patients have been reported with late-onset CMC concomitant with thymoma, polymyopathy reminiscent of myasthenia gravis, and normal serum immunoglobulin levels (Table I A). Analysis of such cases may provide further clues to the pathophysiological mechanisms. The purpose of this paper is to report a similar patient with normal cellular and humoral immune function but having defective neutrophil function.

METHODS

Cell-mediated immunity was studied as described in an earlier publication (24).

Nitroblue tetrazolium reduction (NBT) test was used, as in the semiquantitative modification of Hultborn & Olling (18).

Bactericidal and candidicidal activities of neutrophil granulocytes were measured by a modification of conventional techniques (27). The test organisms used were *Staph. aureus* Oxford 502 A, a serum-resistant *E. coli* strain, and *C. albicans*.

CONTROLS

The neutrophil functions of three patients, 26-38 years old, with myasthenia gravis were studied for comparison. They had all been operated on for thymoma following the diagnosis of the myopathy. All had to take pyridostigmin. None of them suffered from candidiasis.

CASE REPORT

F. S. was a reporter, born in 1907. He had always been healthy, and had not displayed any abnormal tendency to infections. In the autumn of 1972 he gradually developed white patches and soreness all over the oral mucosa including that under his complete dentures. In February 1973, a swelling appeared on his tongue and lips. Concurrently, reddened infiltrated pustular plaques erupted in the face, neck, some fingers and the lower part of the abdomen (Fig. 1). Two fingernails on one hand were thickened, ridged and discoloured. These symptoms have since persisted.

C. albicans was found in repeated cultures from all affected skin and mucosal lesions, and histopathologically pseudohyphae were seen penetrating down into the upper layers of the epithelium. Topical treatment of the mouth with nystatin, chlorhexidine, gentian violet and amphotericin B was of only temporary benefit, as was application to the skin lesions of several antifungal agents (both alone and combined with corticosteroids). Nystatin orally had no obvious effect.

The patient was hospitalized in the autumn of 1973. Physical examination was essentially normal except for the cutaneous and oral changes. The laboratory data are given below. A pulmonary X-ray disclosed a mass in the anterior mediastinum. Exploratory thoracotomy in

Table I.

Patient	Sex	Age at onset (years)	First symptom of the triad	Delayed skin test to candida	Author
A. Chronic mucocutaneous candidiasis, thymoma and myasthenia gravis					
1.	♂	33	Candidiasis	Neg.	Green & Booth (15)
2.	♀	43	Myasthenia	Not done	Anning (2)
3.	♀	51	Candidiasis	Not done	Montes et al. (25)
4.	♀	58	Candidiasis	Neg.	Schoch (29)
5.	♀	41	Myasthenia	Neg.	Montes et al. (26)
6.	♀	ca. 40	Myasthenia	Neg.	Burstein (9)
7.	♂	30	Myasthenia	Pos.	Rycroft et al. (28)
8.	♂	63	Myasthenia	Neg.	Rycroft et al. (28)
9.	♂	66	Candidiasis	Pos.	Lindholm et al.
B. Chronic mucocutaneous candidiasis and thymoma					
10.	♂	42	Candidiasis	Neg.	Baer et al. (3)
11.	♀	67	Candidiasis	Neg.	Maize & Lynch (23)
12.	♀	60	Candidiasis	Neg.	Rycroft et al. (28)
13.	♂	59	Thymoma + candidiasis	Not done	Rycroft et al. (28)

November 1973 demonstrated an orange-sized encapsulated thymoma which was excised radically. The rest of thymus was also removed. Histopathologically, the tumour was dominated by small lymphocytes. Large reticuloid cells occurred sparsely. There was no noteworthy cellular pleomorphism or increased mitotic activity.

The postoperative course was uncomplicated. How-

ever, severe muscular fatigue, especially of facial and masticatory muscles, appeared 2 months later. Intravenous injection of edrophonium (Tensilon®, Hoffmann-La Roche & Co. AG, Switzerland) brought rapid relief of symptoms. His muscle symptoms could be controlled with oral pyridostigmin bromide (Mestinon®, Hoffmann-La Roche & Co. AG, Switzerland). When questioned, he reported having felt slight weakness in the muscles of the face and arms and some difficulty in swallowing for 2-3 months before the thymectomy.

Following the operation, not only did the oral and skin lesions grow larger and approximately 30% of the body area become covered, but the lesions also changed character. They were now less exudative, with scaling, reddened and only slightly infiltrated plaques without pustules. Nevertheless, all lesions produced *C. albicans* on cultures. Their resistance in vitro to the topical antifungal agents used (mostly Nystatin and Vioform) has been repeatedly examined during the disease period. They have always been found sensitive.

In the summer of 1975 treatment with transfer factor (prepared as described by Lawrence & Al.-Askari) (21) was attempted, the agent being administered subcutaneously once weekly for 8 weeks. The amount of transfer factor prepared from 400 ml of blood was given each time. No clinical effects could be discerned.

As the skin lesions were so extensive, so resistant to therapy, and both physically and mentally very annoying to the patient, a trial was made in December 1975 with oral administration of 5-fluorocytosin (Ancotil®, Hoffmann-La Roche & Co. AG, Switzerland), about 10 g daily for 16 days. Most of the skin lesions promptly disappeared. The patient was then immediately started on clofazimine (Lamprene®, Ciba-Geigy A.G., Switzerland), a drug known to promote phagocytosis of neutrophils and macrophages in vivo and in vitro (5, 6). After 3 days, however, there was a rapidly developing, severe relapse.

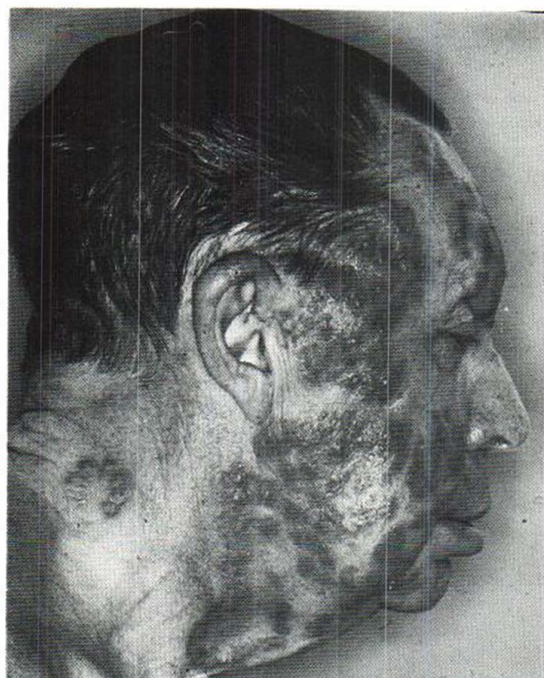


Fig. 1. The face of the patient before thymectomy.

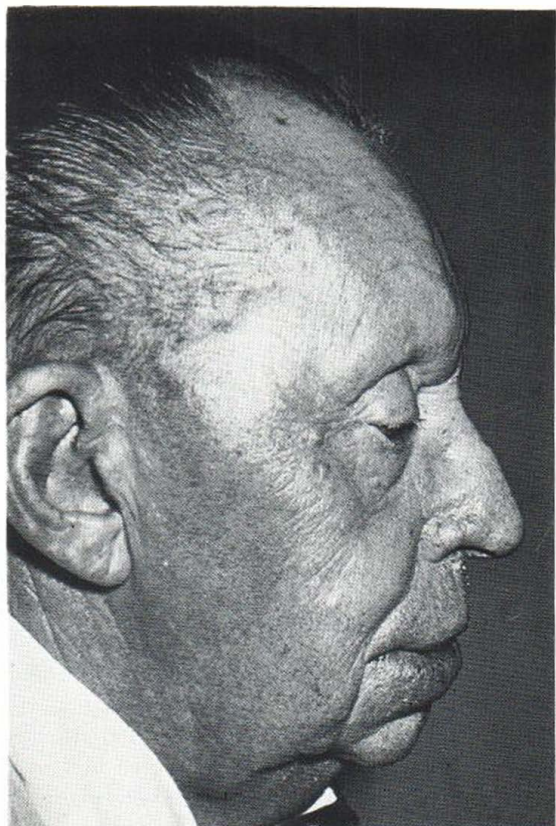


Fig. 2. Following oral therapy with 5-fluorocytosine.

Lamprene was discontinued. The relapse turned into a rebound phenomenon and treatment with 5-fluorocytosine was recommenced. The dosage was monitored continually by determination of the serum concentrations of the antifungal agent. After a month of this there was a sudden, complete heart blockage, so a pacemaker was implanted. The patient had been on 5-fluorocytosine for 5½ months when he suddenly dropped down dead after a fishing expedition. Meanwhile the skin lesions had largely disappeared (Fig. 2). There remained merely some verrucose, scaling lesions on the volar aspects of the fingers, and normal nails had begun to grow out. The lips and tongue were less swollen but still exhibited some white plaques on the oral mucosa. The myasthenia had gradually improved during the early months of 1976 and it had been possible to discontinue pyridostigmin therapy entirely.

At the autopsy, no recurrences of the thymoma were to be seen. The cause of death was acute myocardial infarction.

Laboratory findings. The blood and urine analyses gave similar findings both before and after the thymectomy.

Complete blood cell count, normal. The following investigations on serum also proved normal: electrophoresis, iron and iron-binding capacity, calcium and phosphorus, electrolytes, creatinine, liver function tests

(bilirubin, alkaline phosphatases, thymol, S-GOT, S-GPT, prothrombin), thyroxin and thyroxin-binding globulin. Oral glucose tolerance test, normal. ESR 12 mm/hr. Blood group O Rh(+). HLA-A2; B7, 27; Cw2. Urine analysis, normal. Normal levels of 17-ketogenic and Porter-Silbersteroids in the urine.

Production of circulating antibody. Antistreptolysin-O and antistaphylolysin titres were normal. Wasserman, slightly positive. TPI-test, Waaler-Rose and antinuclear factor, negative. LE-cells not found. Immunofluorescent test for serum antibodies against striated muscle was positive in titre 1:80 (this analysis was performed after onset of muscle symptoms). *C. albicans* serum antibodies: complement-fixing positive in titre 1:15, and in immunodiffusion, positive in titre 1:10. Increased serum concentration of immunoglobulin A (400 mg/100 ml) and E (360 u/ml) and normal concentrations of immunoglobulins G and M.

Cell-mediated immunity. The following investigations gave normal results: the relative proportion of T and B lymphocytes; ³H-thymidine uptake by lymphocytes stimulated with phytohaemagglutinin, concanavalin A, pokeweed mitogen. PPD, *Candida albicans* extract, varidase and mumps antigen. The leukocytes did not migrate in the presence of *C. albicans* extract and PPD. Sensitization in vivo to DNCB was successful. Intradermal skin tests to *Candida* (1/100, Hollister-Stier) and PPD (2 T.U.) were positive (read after 48 and 72 hours). Similar results were obtained before and after the thymectomy. Treatment with transfer factor did not influence the outcome of the tests in vitro.

Neutrophil function. Neutrophils from the 3 patients with myasthenia gravis but without candida infection performed normally in: NBT-tests, and phagocytic killing of *Staph. aureus* (95, 80, 50% of the bacterial inoculum killed) and *E. coli* (95, 90, 80%).

The present patient exhibited normal number and light microscopic appearance of granulocytes at repeated examinations. Myeloperoxidase activity (histochemical method) was normal.

The following granulocyte tests were performed several times during the patient's last year (i.e. after the thymectomy). NBT-test: normal. As long as the candidal infection flourished, no killing of *Staph. aureus* was achieved with patient leukocytes in patient serum (4 tests) and only slight killing (30, 20, 0%—3 tests) with patient leukocytes in pooled normal AB Rh+ serum. Unfortunately our technique does not distinguish intracellular living bacteria from extracellular ones. Later, the test was performed once during the administration of 5-fluorocytosine. At this time, he had been taking it for 5 months, with excellent results. Now his granulocytes performed normally against *Staph. aureus* in autologous serum (90% killing) and in pooled normal AB Rh+ serum (60% killing). Tests against *E. coli* consistently gave normal results (95, 90, 95%).

Significant phagocytic killing of *C. albicans* was obtained with patient leukocytes in both patient and normal serum (50–70%; three tests). Even in non-tumbling tubes containing leukocytes, serum and *Candida*, a reduction of colony-forming units was obtained. No reduction was recorded with serum alone.

DISCUSSION

The clinical symptoms presented by this patient in combination with the presence of anti-skeletal muscle antibodies and the prompt response to parenteral edrophonium chloride establish the diagnosis of myasthenia gravis. In this disease, a hyperplastic thymus is common, and a thymoma is present in about 10% of the patients (10). The concomitant presence of chronic mucocutaneous candidiasis in a patient with myasthenia gravis and thymoma is rare, however: 8 patients from the literature are presented in Table 1A. In addition, 4 cases of CMC have been found in patients with thymoma but without myasthenia (Table 1B).

The development of widespread, refractory cutaneous candidiasis indicates that an acquired systemic defect is present. Cellular hypersensitivity to *C. albicans* has experimentally been demonstrated to be of primary importance for host resistance to superficial candidiasis, as compared with serum antibody (7). This explains the candidiasis seen in patients with congenital thymic abnormalities and during immunosuppressive treatment. CMC with onset early in life is associated with varying patterns of abnormalities of cell-mediated immunity (33), though these could be due rather to suppression of the cellular immune response caused by the candida infection (8, 20). The delayed skin reaction to candida, absent in 5/6 patients reported in the literature with late-onset CMC combined with thymoma and myasthenia gravis (Table 1A), also points to altered cell-mediated immunity. The same uncertainty exists, however, about causal relationships (*vide supra*).

Reports of the rare concurrence of myasthenia gravis, thymoma and CMC suggest that a causal interrelationship may exist. Myasthenia gravis is accompanied by autoimmune phenomena (32), and the thymus has a central role in the immune system. Moreover, it has recently been suggested that myasthenia gravis is the result of overproduction of a thymic hormone, thymopoietin (14). The present patient, however, had normal *in vivo* and *in vitro* responses to candida antigen, indicating an intact humoral and cellular immunity. However, it remains to be seen whether overproduction of a thymic substance, normally responsible for inducing differentiation of thymocytes, can cause malfunctions within the immune system.

It is therefore of interest that a few patients with

CMC have recently been reported to have disorders of leukocyte function: leukocyte myeloperoxidase deficiency (22), defective neutrophil and/or mononuclear chemotaxis (11, 12, 16, 30), reduced granulocytic chemotactic and phagocytic capacities (4), and subnormal candidicidal capacity (28). As long as his cutaneous infection flourished, the present patient's neutrophils exhibited poor killing of *Staph. aureus*, irrespective of whether fresh autologous or homologous serum was used as opsonins. The neutrophil dysfunction persisted for more than 1 year, in contrast to 3 thymectomized patients with myasthenia gravis. The clinical significance of this leukocyte deficiency is not clear, however: (i) the patient had no problems with bacterial infections, (ii) a similar leukocyte defect has been found in about 10% of healthy blood donors (27), (iii) the granulocytes performed normally when the skin lesions had been eradicated. We are not aware of studies suggesting that 5-fluorocytosine restores the disturbed microbicidal power of granulocytes. It may therefore be that our patient's neutrophil dysfunction was associated with his cutaneous fungal infection in the same way as the transiently impaired bactericidal capacity reported in severe bacterial and viral infections and in burn injury (1, 19, 31).

No impairment of phagocytosis and killing was noted when *Candida* was used as the test organism. Chemotaxis was never analysed.

The effect of 5-fluorocytosine was excellent. This preparation is also effective in topical usage (13), but it has appeared that such administration can quite easily induce resistant strains of *Candida* (17). In principle, 5-fluorocytosine should therefore be reserved for oral use and then only in severe infections.

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