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Thyrotoxicosis associated with Aspergillus thyroiditis in chronic granulomatous disease

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THIS COMMUNICATION reports the successful treatment of *Aspergillus* thyroiditis in a boy with chronic granulomatous disease and describes the sequence of alterations in thyroid function produced by the infection. Although the anticipated signs and symptoms of acute suppurative thyroiditis were documented, the abnormalities of thyroid function were those generally considered to be characteristic of subacute thyroiditis.

CASE REPORT

The patient, an 11-year-old Caucasian boy, has been followed at the University of Missouri Medical Center since 10 months of age for recurrent infectious illnesses. During the first year of life he experienced recurrent cervical adenitis which was associated with spontaneous drainage of sterile purulent material. At 6 and 7 years

of age he was treated with amphotericin B for a generalized, granulomatous pneumonia. Although an organism was not cultured from lung or tracheal aspirates, *Aspergillus* was recovered concomitantly from a cerebellar abscess in a sibling. At 10 years of age he was successfully treated for pneumonia resulting from *Bacterium anitratum*.

A diagnosis of chronic granulomatous disease was made on the basis of studies of neutrophil function. Stimulated cultures of patient neutrophils failed to reduce nitroblue tetrazolium¹ or

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to effect normal rates of killing of *Staphylococcus aureus*, *E. coli*, and *Pseudomonas*.^{2, 3} Sensitization to dinitrochlorobenzene was successfully induced and normal delayed hypersensitivity to the intracutaneous injection of histoplasmin antigen was observed. A brother of the patient died at 9 years of age with chronic pulmonary disease; although sterile by culture, his lymph nodes and lung demonstrated prominent granuloma formation. A second brother, 9 years of age, has experienced recurrent infections of lung and brain. His granulocytes neither reduce nitroblue tetrazolium normally nor have normal bactericidal activity. A third brother died at 3 years of age with acute lymphocytic leukemia. This child had no clinical or histologic evidence of chronic granulomatous disease. Seven siblings are well.

Episode of thyroiditis. At 11 years of age the patient developed a tender, firm mass in the anterior neck. Concomitantly, he had daily temperature elevations of 101 to 104° F., increased purposeless activity, and nervousness. He denied dysphagia, loss of appetite, breathlessness, or change in bowel habits. The blood pressure was 114/60 mm. Hg, and the resting pulse 116 beats per minute. The skin was warm and moist.

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Table I. Summary of thyroid function studies

Observation	Normal range	Weeks after onset of thyroiditis							
		0	3	6	8	12	20	24	39
PBI	4-8 $\mu\text{g}\%$ *	18.0	13.6	9.0	8.0	8.0	7.0	6.9	5.3
T ₄	3-7 $\mu\text{g}\%$ *	11.9	9.8	4.9	5.3	—	5.7	4.9	5.8
BMR	-10 to +10%*	+26	+19	-6	-1	—	—	-1	—
I ¹³¹ uptake	5-25%† (24 hr.)	< 1%	—	2%	—	—	—	12.6%	—
Thyroid antibody titer	1:5-1:250*	1:5	—	1:5	—	—	—	—	1:5
ESR	0-20 mm./hr.	47	52	44	30	22	25	19	18

Abbreviations: PBI = protein-bound iodine, T₄ = tetraiodothyronine (Murphy-Pattee), BMR = basal metabolic rate, I¹³¹ uptake = radioactive iodine uptake, ESR = erythrocyte sedimentation rate.

*Normal range cited by Ingbar.⁷

†Range observed in normal subjects in our radioisotope laboratory.

The thyroid gland, 6 × 5 cm. in size, was firm and tender. The overlying skin was warm and erythematous. No thyroid nodules or cervical nodes were palpated. The eyes converged normally and no lid lag was detected. Deep tendon reflexes were hyperactive. The fully extended arms and hands demonstrated a fine tremor. No other focus of infection was identified.

Initial laboratory data included a hemoglobin of 11.4 Gm. per 100 ml. and white blood cells 10,600 per cubic millimeter with 60 per cent neutrophils and 40 per cent lymphocytes. The erythrocyte sedimentation rate was 47 mm. in one hour. Chest roentgenograms were normal. Cultures of blood, sputum, and urine were sterile. The protein-bound iodine (18 μg per 100 ml.), serum T₄ (Murphy-Pattee, 10.9 μg per 100 ml.), and basal metabolic rate (+ 26 per cent, afebrile) were increased. Despite clinical and laboratory evidence of hyperthyroidism, the uptake of I¹³¹ by the thyroid was less than 1 per cent. Thyroid antibodies were not detected in significant titers by tanned red cell agglutination. Serum cholesterol concentration was 165 mg. per cent.

Failure of the gland to trap iodine suggested that the thyrotoxic state was not due to augmented hormone synthesis. As a result, anti-thyroid medications were not given. The gland increased in size to 8 by 6 cm. and developed fluctuance. Twenty-nine days after the onset of thyroid swelling, the mass was incised. The 10 ml. of purulent material that was drained contained *Aspergillus fumigatus* which was sensitive to amphotericin B at a minimal inhibitory concentration of 0.625 μg per milliliter of serum. A 5 week course of amphotericin B effected return of the thyroid gland to normal size and a resolution of signs and symptoms of hyperthyroid-

ism. During the 5 weeks of treatment a level of 1.25 μg amphotericin B per milliliter of serum was achieved and a total dose of 691 mg. was administered.

Sequential changes in tests of thyroid function are summarized in Table I. Six weeks following surgical drainage and institution of antibiotic therapy, thyroid function was normal. Thyroid uptake of I¹³¹ was normal 6 months after the onset of thyroid disease. Neither clinical hypothyroidism nor decrease in thyroid activity by laboratory parameters has been observed.

DISCUSSION

Despite the frequency of pyogenic infections in children, acute suppurative thyroiditis is infrequently encountered in patients under 15 years of age. *Aspergillus* as a cause of suppurative thyroiditis has not been previously described. Invasion of the thyroid gland by an organism of low virulence was undoubtedly facilitated by deficient antibacterial activity of patient neutrophils.

The typical clinical features of acute suppurative thyroiditis were illustrated by the patient: thyroid swelling, inflammation, and suppuration were prominent, fever was pronounced, hyperthyroidism was clinically obvious, and *Aspergillus fumigatus* was recovered from the gland. The increase in protein-bound iodine, T₄, and basal metabolic rate were in keeping with the clinical observations.⁴⁻⁶ On the other hand, the decrease in I¹³¹ uptake and the disproportionate increase in protein-bound iodine are features which are generally associated with subacute thyroiditis.⁷ Because the gland failed

to trap iodine, it may be concluded that the hypermetabolic state was due to the escape of stored thyroid hormone rather than to accelerated hormone synthesis. Both clinical and laboratory evidence of hyperthyroidism resolved 6 weeks after the onset of thyroiditis and 2 weeks after surgical drainage of the thyroid. The capacity of the gland to trap iodine was not regained until sometime between the sixth and twenty-fourth week. Failure to observe a decrease in thyroid activity prior to the return of the radioactive iodine uptake to normal suggests that hormone stores were not exhausted during the period of acute suppuration.

SUMMARY

Acute suppurative thyroiditis due to *Aspergillus fumigatus* in a child with chronic granulomatous disease was successfully treated with surgical drainage and amphotericin B. The acute phase of the infection was characterized clinically by hyperthyroidism, chemically by an increase in protein-bound iodine and T_4 , and functionally by a decrease of I^{131} uptake. Return to an euthyroid state occurred 6 weeks after the onset of thyroiditis. Recovery of the gland's ca-

capacity to trap iodine was not noted until after the sixth week. Thirty-nine months after the onset of thyroiditis, thyroid function is normal.

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Screening test for methylmalonic aciduria utilizing urine-impregnated filter paper samples

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METHYLMALONIC aciduria is an in-born error of metabolism characterized by severe metabolic acidosis in the newborn period and followed by mental retardation, episodes of acidosis, and growth arrest.¹ The disease is the result of impairment in the conversion of methylmalonyl CoA to succinyl CoA, resulting in the appearance of large amounts of methylmalonic acid in the blood and urine. A degree of therapeutic success has been achieved with dietary restriction of the propionyl CoA and methylmalonyl CoA, precursors of L-isoleucine and L-valine. Vitamin B₁₂ therapy is helpful in some,^{2, 3} but not in others.⁴

Giorgio and Plaut⁵ have developed an analytic method for methylmalonic acid using ion exchange isolation followed by diazotized *p*-nitroaniline reagent to form a