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Malabsorption, Megaloblastic Anemia and x-Linked Immunodeficiency with hyper IgM*

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Gastrointestinal symptoms such as acute or chronic diarrhea, malabsorption causing concomitant failure in gaining weight and in normal growth, steatorrhea, hematemesis, dysphagia are characteristics of certain immunodeficiency syndromes. Twenty to fifty percent of patients with common variable immunodeficiency syndrome have gastrointestinal disorders.[1-4] Although gastrointestinal diseases are rare in x-linked hypogammaglobulinemia,[1,2] they are frequently reported with selective IgA deficiency and combined immunodeficiency diseases.[5,6]

To our knowledge no case of malabsorption with x-linked immunodeficiency with hyper IgM (H.IgM) has been reported. We have therefore presented here an interesting patient with H.IgM who showed special hematological and gastrointestinal dysfunctions.

Case History: M.T. a 12 year old boy, was admitted to the hospital with a six year history of recurrent pneumonia, otitis media, diarrhea and failure in gaining weight despite of good appetite. He had had productive cough for the past 4 years. He had three healthy sisters and there was no family history of immunodeficiency. On physical examination the positive findings were, growth retardation (his height and weight were below the third percentile) bilateral crepitant rales on both lung fields, and hepatosplenomegaly. Radiological examination showed chronic maxillary sinusitis and bilateral bronchiectasis.

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Hematological, gastrointestinal and immunological findings are tabulated in Tables I-IV.

Methods

Serum immunoglobulin determinations,[7] E[8], HEA, HEAC[9] rosettes, surface immunoglobulins (SIg)[10] and lymphocyte blastic transformation[11] tests were performed with the methods reported elsewhere. Secondary antibody response to tetanus and diptheria toxoids was detected by hemaglutination test described by Levine et al.[12]

After ficoll-hypaque gradient separation, peripheral blood lymphocytes were cultured with and without pokeweed mitogen (PWM) (to 10^6 lymphocytes per ml of culture, 10 µg PWM was added) for six days at 37°C in 5 % CO_2 in air. Cytocentrifuge smears were prepared and plasma cell generation was detected by fluorescein conjugated antisera (Behring-Werke IgG, IgM, IgA and polyvalent) using a Leitz model Orthoplan immunofluorescent microscope.

Lymphnode biopsy was performed 5 days after the antigenic stimulation with diptheria and tetanus toxoids. A jejunal biopsy was done with a pediatric size Crosby-Kugler capsule and was examined under the light and immunofluorescent microscope.

A seventy-two hour quantitative fecal fat excretion and 5 hour urinary excretion of D-xylose following the ingestion of 25 g d-xylose were determined.[13, 14] The gastric acidity was tested after 12 hour fasting. Multiple stool, duodenal and jejunal juice specimens were examined for Giardia Lamblia.

Results

The patient's IgM values were two standard deviations above the normal. The serum electrophoresis and immunoelectrophoretic analyses showed that IgM was polyclonal. IgA was absent, IgG and IgE levels were decreased. Isohemagglutinin titers were high and the antibody response to tetanus and diptheria toxoids was defective (Table IV).

The number of B cells bearing surface IgM was slightly increased. Despite almost normal percentage of surface IgG and IgA bearing cells, the number of IgG and IgA containing plasma cells was severely depressed after PWM stimulation. In cellular immunity there was not any significant changes as can be seen from Table III.

The patient had a megaloblastic anemia, a reticulocyte crisis occured following vit. B_{12} treatment (1 µg/I.M.) and the Hb value turn-

TABLE I

HEMATOLOGICAL FINDINGS

	Hb (gm/dl)	Reticulocyte count %	Bone marrow	Serum folic acid (ng/ml)	Serum Fe Serum Fe (ug/dl) binding Cap.	WBC/mm³	Thromb. C/mm³
Before B_{12} therapy	6.3	0.1	megaloblastic changes	5.9 N 5	268 341	7800-19300	200000
twelve days after B_{12} therapy (1 ug/I.M.)	10.6	2.4			39/289	9000	400000

TABLE II

FINDINGS RELATED TO MALABSORBTION

	Prothrombin time/PTT	Vit A	Caroten	PH of the Gastric juice	Stool pH	Sweat test (Cl/mEq/)	24 hours faecal fat excretion	D-xylose excretion	Jejunal biopsy
	19 sec 165 sec.	22.5 ug/dl	0.29 ug/dl	7.0	6.5	36 39	24.5 mg/	12.9 %	flattening of the villi and mononuclear cell infiltration in lamina propia.
Normal values	12sec/80 sec	40 ug/dl	0.90 ug/dl	5	40	40	5 gr	20 %	

TABLE III

CELLULAR IMMUNITY AND BIOPSY FINDINGS

Skin Tests*				E rosettes	lymphoblastic transformation** (stimulation index)				
PHA	Cand	SKSD	PPD	(%)	PHA	Cand	SKSD	Lymph node biopsy	Jejunal biopsy
+	−	−	−	49	143	5.8	0.8	germinal centers, and secondary follicules were present. immunofluorescent staining showed: only IgM containing plasma cells.	Immunofluorescent staining showed infiltration with IgM (+) plasma cells IgA and IgG containing plasma cells were absent.
Normal values				65±6	20	2	2		

* An induration greater than 5 mm at 48 hours is considered positive

** Stimulation index: CPM stimulated/CPM unstimulated

TABLE IV

HUMORAL IMMUNITY FINDINGS

	Serum Ig's (mg/dl)				Isohemagglutinins				Surface Ig (%)				Plasma cell generation after PWM stimulation				Antibody response	
Date	IgG	IgA	IgM	IgE	anti-A	anti-B	HEA%	HEAC%	P*	IgG	IgM	IgA	P*	IgG	IgM	IgA	Dipt.	tetanus
				(I.U.)														
March 14, 77	125	0	297	10U>	1/512	1/128	6.5	7	13	3	11	1	6	0.5	7	0	—	—
May 16, 77	290	0	375															
Oct 10, 77	165	0	305															
Normal ± S.D. values	1200±370	232±58	114±34				14±5	16±6	15±4	9±5	7±3	3±2	11 (8-17)**	6 (4-8)	4 (3-7)	2 (1-5)		

* Polyvalent (IgG+IgA+IgM)

** Range

ed to normal in twelve days (Table I). Gastrointestinal absorbtion tests showed severe malabsorption with steatorrhea (Table II). Biopsy findings are shown in Table II-III.

Discussion

The gastrointestinal and hematological abnormalities associated with immunodeficiencies are complex and variable. Giardia Lamblia is the most common recognized cause of chronic diarrhea, vit B_{12} deficiency and malabsorption in immunodeficiency syndromes, but the pathophysiology of these disorders is not clearly understood.[1, 3, 4, 15] We could not demonstrate any trophozoites or cystes of Giardia Lamblia in the various stool samples, in the duodenal-jejunal juices and in the jejunal biopsy material. Also after a ten day course of metronidazole (flagyl) therapy there was no improvement in absorption.

There was an increase in mononuclear cell infiltration and a flattening of the villi in the jejunal biopsy sections. Immunofluorescent staining showed that these cells contained IgM but not IgA or IgG. Although the jejunal biopsy and high serum IgM values are compatible with gluten sensitive enteropathy,[16] our patient did not respond to a gluten free diet which was carried out for a period of three weeks. In addition serum IgA was absent and serum IgG was low and his secondary antibody response was severely defective.

Infiltrative processes of the intestinal wall which are encountered in lymphoma, alpha heavy chain disease, multiple myeloma and macroglobulinemia, but these disorders are almost always associated with monoclonal macroglobulin or paraproteins.[15-18]

The pathogenesis of H.IgM is not clearly understood.[19-25] In our patient the result of the SIg and plasma cell generation tests suggest either a helper cell defect or an increase in supressor cells. In spite of normal SIg bearing IgG and IgA cells, the plasma cell generation of these types was defective (Table IV). It has been shown that suppressor cells play an important role in the pathogenesis of some common variable immunodeficiency cases.[26]

It is reported that the transfer of intermediate doses of suppressor cells into normal chickens may change the immunoglobulin levels resembling type I dysgammaglobulinemia.[27] Clinical histopathological and immunological findings of our patient were compatible with the acquired form of type I dysgammaglobulinemia.[1-4, 28]

The exact mechanism of the malabsorption syndrome, steatorrhea and megaloblastic anemia in association with H.IgM in our case has yet to be elucidated, although infiltration of the jejenum with mononuclear cells may contribute to the pathogenesis of his illness.

REFERENCES

1. Ament, M. E., Ochs, H. D. and Davis, S. D.: Structure and function of the gastrointestinal tract in primary immunodeficiency syndromes. A study of 39 patients. Medicine 52: 227, 1973.
2. Rosen, F. S. and Janeway, C. A.: The gammaglobulins III The antibody deficiency syndromes New. Eng. J. Med. 275: 709, 1966.
3. Ament M. I.: Immunodeficiency syndromes and gastrointestinal disease. Ped. Clin. of North. Am. 22: 807, 1975.
4. Brown, W. D., Butterfield, D., Savage, D., and Tada, T.: Clinical microbiological and immunological studies in patients with immunoglobulin deficiencies and gastrointestinal disorders. GUT 13: 441, 1972.
5. Amman, A. J. and Horg, D.: Selective IgA deficiency. in Stiehm, E. R. and Fulginiti V. A. (eds) Immunologic disorders in infants and children Phildadelphia W. B. Saunders Co. 1973, pp. 199.
6. Hitzig, W. H.: Congenital thymic and lymphocytic deficiency disorders. in Stiehm, E. R. and Fulginiti V. A. eds. Immunologic disorders in infants and children Philadelphia W. B. Saunders Co. 1978, pp. 215.
7. Fahey, J. L. and Mc Kelvey, E. M.: Quantitative determination of serum immunoglobulins in antibody agar plates. J. Immunol 94: 84, 1965.
8. Jondal, M., Holm, G., Wigzell, H. N.: Surface markers on human T and B lymphocytes I. A large population of lymphocytes forming non immune rosettes with sheep red blood cells. J. Exp. Med. 136: 207, 1972.
9. Schiff, R. I., Buckley R. H., Gilbertson, D. B., Metzgar, S.: Membrane receptors and vitro responsiveness of lymphocytes in human immunodeficiency, J. Immunol. 112: 376, 1974.
10. Kincade, R. W., Lawton, A. R., Cooper, M. D.: Restriction of surface immunoglobulin determinants to lymphocytes of the plasma cell line J. Immunol. 106: 1421, 1971.
11. August, C. S., Levey, R. H., Berkel, A. I., Rosen F. S., Kay, H.E.M.: Establishment of of immunological competence in a child with congenital thymic aplasia by a graft of fetal thymus Lancet 1: 1080, 1970.
12. Levine, F., Wyman, L., Brodecrick, E. J. and Ipsen J. Jr.: A field study in triple immunization (diptheria, pertussis, tetanus). J. Pediatr. 57: 836, 1960.
13. Weijers, H. A. and Van de Kamer, H. J.: Coeliac disease. Criticism of the various methods of investigation. Acta Paediat. Scand. 42: 24, 1953.
14. Meites, S. Faulkner, W. S: Manual of practical and general procedures in clinical chemistry C. C. Thomas Pub. Spring field III. 1962, p. 231.
15. Ament, M. E. and Rubin, C. E.: Relation of Giardiasis to abnormal intestinal structure and function in immunodeficiency syndromes. Gastroenterology 62: 216, 1972.

16. Taylor, K. B.: Gastrointestinal and liver diseases ed. by. Fundeberg H. H. in Basic and Clinical Immunoloy Lange Med. Publ. California 1976, pp. 456.
17. Eidelman S. Parkins R. A., Rubin, C. E.: Abdominal lymphoma presenting as malabsorption. Medicine 45: 111, 1966.
18. Seligmann, M., Danon, F. Hurez, D., Mihaesco, E., Preudhomme, J. L.: Alpha chain disease: a new immunoglobulin abnormality. Science 162: 1396, 1968.
19. Goldstein W. B., Poker N: Multiple myeloma involving the gastrointestinal tract. Gastroenterology 51: 87, 1966.
20. Bradley, J. Hawkins C. F., Rowe, D. S., Stanworth D. R. Macroglobulinemia and steathorrhea Gut 9: 564, 1968.
21. Stiehm, E. R., Fudenberg H. H.: Clinical and immunologic features of dysgammaglobulinemia type I. Am. J. Med. 40: 805, 1966.
22. Masi, M.: Dysgammaglobulinemia tipe I. Minerva Pediatrica 23: 885, 1971.
23. Rosen, F. S., Craig, J. M., Wawler, G., Janeway, C. A.: The dysgammaglobulinemias and x-linked typmic hypoplasia. Brith Defect Orig. Art. Series 4: 67, 1968.
24. Goldman, A. S., Goldblum, R. M.: Primary deficiencies in humoral immunity. Ped. Clin. of North Am. 24: 277, 1972.
25. Goldman A. S., Riteman, S. E., Haustan, E. W., Sidwell, S.: Bratcher, R. Levin, W. C.: Dysgammaglobulinemic antibody deficiency syndrome. J. Pediat 70: 16, 1967.
26. Waldmann, T. A., Broder, S.: Suppressor cells in the regulation of the immune response in Progress in clinical Immunology, Vol. 3 ed by. Schwortz R. S. Grune and Stratton New York 1977, pp. 155.
27. Waldmann T. A., Blaese R. M., Samuel, B. Krakauer, R. S.: Disorders of suppresser immunoregulatory cells in the pathogenesis of immunodeficiency and autoimmunity. Ann. Internal. Med. (in press)
28. Twomey, J. J. Jordan P. H., Jarrold, T., Trubowitz, S., Ritz N. R. Conn H. O.: The syndrome of immunoglobulin deficiency and pernicious anemia Am. J. Med. 47: 340. 1969.