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SMALL INTESTINAL LYMPHOMA AND ALPHA HEAVY CHAIN DISEASE REVIEWING 15 ADVANCED CASES AND COMMENTING ON THE RESULTS OF THERAPY

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Introduction

The Heavy Chain Disease or to put it more accurately: the Immunoproliferative Small Intestinal Disease (IPSID) or as more anciently called: The Mediterranean Disease is attended with such common symptoms as diarrhea,weight loss, gastric pains, and the clubbing of fingers and toes. The disease occurs in the Mediterranean region and in the developing countries. The etiology is unknown;but there seems to be some vague relationship between the disease and infestation with bacteria or parasites particularly the Giardia (37-43). In this disease lymphoplasma cells infiltrate into the membrane and the proximal wall of the small intestine. In the course of its advancement, it takes the form of an invasion to the lymphatic glands of the mesenterium and the abdominal viscera. The neoblastic cell level in the patient's serum rises as the result of the uncontrolled synthesis of Alpha Heavy Chain and the discharge of such cells into the plasma.

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In this study of 15 advanced cases referred to our center for treatment, the effects of the therapy and remission periods are reviewed.

The disease was descirbed for the first time by Seligmann in the year 1968 (24) and was found to be the commonest type of the heavy chain diseases (17,16,12) and in comparison with other heavy chain diseases, the ailment seems more likely to affect young people and children (17,25) and tends to affect the 10 to 30-year age group more commonly than others. The involvement area varies depending on the infiltration point of the Ig A discharging cells which is often in the small intestine(25,18, 17,2) and rarely the respiratory system(26,4,3).Symptoms include acute syndrome of absorption disorder such as diarrhea, gastric pains, asthenia, and severe weight loss. Fever is uncommon and the patient might show signs of intestinal closure. The disease might deteriorate or improve spontaneously or might retreat for some time.

Physical examination might reveal a distension of the abdomen and in advanced cases a feeling of the lymph nodes in the abdomen but hepatospleenomegaly and peripheral lymphoadenopathy are rare (9,8,5). A clubning of fingers and toes also occurs (22,21). Pathologically the disease occurs predominantly in the second,third, and fourth sections of the duodenum with occasional involvement of the jejunum. The involvement of ileum or the entire intestine is very rare indeed (22,21) so is the involvement of the stomach and the large intestine. Intestinal damage is usually diffused affecting the entire depth of the membrane. Occasionally lesions are nodular presenting a cobblestone pattern (22).

There are microscopic changes of the intestinal membrane surface consisting of the transformation and cubing (loss of nuclear polarity) of the intestinal membrane epithelium (21). The emigration of lymphocytes from the epithelial area and the ulceration of the membrane leads to reactive inflammation combined with cellular infiltration (22,21).

The stenosis of Lieberkuhn crypts and the dilatation and closure and effacement of the vilosities are established symptoms showing the acuteness of the lesions and mucosal infiltration. (22,21).

FROM PATHOGENESIS VIEWPOINT:

This disease is usually seen among the underprivileged class of the society and is more prevalent among the peoples of the Middle East, Mediterranean area, south and Central Africa, South East Asia, and South and Central America.

Economic poverty, substandard hygiene, infestation with parasites and recurrent infections during childhood are considered to be among contributing factors. No particular food or pathogen has yet been identified as a causing agent (27,23,22,21).

Clinical Semiology

Maximum involvement occurs in the second or third decade of life. There is no difference between men and women as regard exposure to the disease, (23,22,21). General and clinical symptoms have been the same, more or less, despite the exhaustive histopathological findings. Notable among all symptoms is chronic diarrhea and more often than nor the disease results in malabsorption, weight loss and gastric pains.

In the past two years we had 15 cases of advanced Mediterranean lymphoma (IPSID) they were referred to us after diagnosis for treatment in the Oncology section of the medical department of Shariat Hospital in Tehran. Clinical Symptoms of the Patients are Summarized in Table I.

Most Common Symptoms	No.of Patients	Percent
Chronic & Intermittent Diarrhea	15	%100
Weight Loss (Exceding %10 of the previous weight	14	%93.3
Belly Pain and Cramp	13	%86.6
Clubbing of Fingers	10	%66.6
Feeling a Mass in Abdomen	8	%53.3
Fever(Often below 38.5°C)	4	%26.6

Table 1, some common clinical symptoms in patients

The patients ages ranged between 19 to 42. There were 8 women and 7 men, all beloning to the under-privileged and low income classes. 11 patients were referred to us after a staging laparatomy. The remaining Four patients presented in the liver invoivement

provied by the pathology
test of the needle biopsy
taken from the liver.
Therefore, laparatomy was
not undertaken in their
case.

A total of six patients were diagnosed to be in Stage III and the rest (9 cases) in stage IV of the disease. The result of laboratory finding as listed in Table II.

Lab. Findings	patients No.	Percent
High values	15	%100
Signs of malabsorption	14	%93.3
Mild hypoalbuminemia	14	%93.3
Mild Anemia	15	%100
Hypocalcemia	12	%80
Feeling of a mass in belly	11	%73.3
Fever	4	%26.6
Alpha Chain	11	%73.3

Table II-Some laboratory findings of the patients

Various methos have been suggested for classification of the disease in terms of the extent of its progress--notably the slaging method of Gallin and that recommended by the UICC. The latter has been used in this study.

C. RECOMMENDED STAGING CLASSIFICATION

Stage O(*)	Benign-appearing lymphoplasmocytic mucosal infiltrate. No evidence of malignancy
Stage I	Diffuse lymphoid infiltration of intestinal muccsa and malignant lymphoma in either intestine or mesenteric lymph nodes but not both.
Stage II	Diffuse lymphoid infiltration of intestinal mucosa and malignant lymphoma in both intestines and mesenteric lymph nodes.
Stage III	Diffuse lymphoid infiltration of intestinal mucosa, malignant lymphoma in abdomen and metastasis to retroperitoneal and/or extra-abdominal peripheral lymph-nodes.
Stage IV	Presence of metastasis in non-contiguous non-lymphatic tissues in addition to abdominal lymphoma.

Unknow Exploratory laparatomy not done, no detectable extraabdomainal disease.

(*) "Pre-malignant" phase of the disease should not be diagnosed short of adequete staging laparotomy. Stage O potentially curable by prolonged antibiotic treatment.

Method of Treatment: Six patients of Stage III were subjected to six souses of CHOP chemiotherpay subsequently being treated with whole-abdominal radiotherapy for 3000 rads of radiation. Patients were then subjected to monthly clinical checks afferwords.

Nine patients in Stage IV were subjected to Chemotherapy along (CHOP). Two of them, because of their large interabdominal mass, were subjected to local radiotherapy. The choice of treatment was made as per the UICC-1981 recommendations (See table 3). Treatment choice as per the stage method and the results appear in Table. IV.

TREATMENT RESULTS

Five cases out of the overall six patients in Stage III presented a complete disappearance of all symptoms after the application of six courses of chemotherapy in CHOP regimen and whole - abdominal radiotherapy (with kidneys sheildings) and registered a general improvement. They were then subjected to monthly checks for 23 months without further treatment.

Another patient 18 months after treatment presented

Stage	Treatment	Results
0	No specific anti-cancer therapy indicated. Majority of patients cured by prolonged tetracycline treatment	curable 80-90 %
I	Radiotherapy alone	curable 40-50 %
II	Radiotherapy followed by 6 cycles of chemotherapy	curable approx. 25%
III	Six cycles of chemotherany followed by radiation therapy. In case of residual disease after radiation therapy, chemotherapy therapy should be pursued	Cure rate is very low-medium. Survival is approximately 18 months
IV	Chemotherapy alone. Radiation therapy may be used to control local bulky disease	Medium survival is approximately 10 months

Table III

Remarks	Remission period after	Treatment Procedures	Patients No.	Stage
Patients Living	23 monts	* Six courses of CHOP whole-abdomen Radio-therapy with 3000 Rad	5	Stage III
Patient Died	18 months	Above procedures	one	
Patients living	15 months	8 courses of CHOP	3	
Patient living	9 months	CHOP 8 courses and 4 courses	one	
Patients living	8 months	CHOP 8 courses followed by another 8 courses	3	Stage IV
Thes two patients did not reapped Nor we have we have an news from them	9 monlhs	8 courses of CHOP Abdomer Radiotherapy with 3000 rad of radiation	one	
		8 courses of CHOP Abdomen Radictherapy with 3000 rad of radiation	one	

Table IV- Chemotherapy courses and remission times of the patients

* CHOP

-Adriamycin 40 mg/m^2 i.v.

-Cyclophosphamide 600 mg/m^2 i.v.

-Vincristine 1.4 mg/m^2 i.v.

-Prednisone 40 mg/m^2/day x 5 p.o.

Repeated every 4 weeks

symptoms of diarrhea, fever, and weight loss and was agains subjected to treatmont with CHOP regimen.Unfortunately however, he developed acute leukopenia, thrombocytopenia, and anemia with severe infection (Septicemia).

Of the nine patients in Stage IV, three responded well to treatment and showed a complete disappearance of the symptoms without further treatment being necessary. However, monthly checks continued for 15 months and they have normal Ig A. Four patients two months after treatment despite showing a normal Alpha HC in the serum developed a recurrence of diarrhea forcing a resumption of the treatment. Patient was subjected to a CHOP regimen administared up to four courses monthly rendering further treatment unnecessary, being reviewed monthly for the past nine months. He is in a good general condition.The other three patients who were also subjected to treatment with CHOP regimen administered up to 8 courses monthly improved generally: diarrhea stopped, weight began to increase and Alpha HC became normal. Monthly checks continued, however. But the patient have not received any medication in the past 8 months.

Two other patients having been subjected to 8 courses of CHOP regimen and whold-abdominal radiotherapy coming monthly visits one patients for nine months and the others for six months and they have normal physical conditions. However, despite having been urged to carry on with the regular monthly visits, they failed to reapperar and we have not heard from them since.

SUMMARY:

The IPSID in its severe cases invades the lymph no-

aes, mesenterium, and abdominal viscera resembling NNL *Low grade). Diarrhea and malabsorption were present in all of the 15 patients under study. Moreover, 14 patients were suffering from obvious weight loss more than 10 peresented mild anemia together with the increased IgA in the serum. Clubbing was also present in two thirds of the patients. Chemotherapy alone or combined with radiotherapy caused rapid regression of the disease. The patients had comparatively long survival. see table 4).

REFERENCES

1-Doe WF et al: Immunodignosis of alpha chain disease. Clin Exp Immunol 36: 189.1979.

2- Frangione B, Fralklin EC: Heavy chain disease: Clinical features and molecular significance of the disordered Immunoglobulin structure: Semir Homatol 10: 53, 1973.

3- Stoop JW et al: Alpha chain diseasse with involvement of the respiratory tract in a Dutch child. Clin Exp immunol 9: 625 1973.

4- Florin-Christensen A et al: Alpha chain disease with pulmonary manifestation. Med J. 2: 413, 1974.

5- Kharazmi A. ot al T and B. Lymphocystes in alpha-chain disease Br J. Cancer 37, 1978.

6- Levin K at al: Primary intestinal lymphoma of western and mediterranean type. Alpha chain disease and massine plasma cell infiltration. Cancer 38: 2511, 1975.

7- Preusd, homme JL et al: Cellular immunoglobulins in human J and heavy chain disease. Clin exp Immunol 37: 282, 1979.

8- Brouet J C et al: Alphachain disease: Evidence for clonal origin of intestinal immunoblastic lymphoma and plasmacytic proliferation. Lancet 1: 861, 1977.

9- Cohen HS et al: New Presentation of alpha heavy chain disease: North American polypoid gastrointestinal Lymphoma. Cancer 41: 1161, 1978.

10-Doe W.F. et al: Radiological and histological findings in six patients with alph-chain disease. Br. J.Radiol 49: 3, 1976.

11- Manousos on et al: Alpha Chain disease with clinical Immunological and histological recovery. Br Mod J. 21409, 1974.

12- Ramboud JC, Matuchansky C: Alph Chain disease.Lancet 1: 1430, 1973.

13- Ramboud JC et al: Natural hisotry of chain disease and the so-called mediteranean lymphoma. Receny Result cancer Res 64: 271, 1976.

14- Roge J et al: Lymphoma Mediterraniane arec maladie des chaines alpha. Patbol Biol. 18: 851,1970.

15- Seligmann M: Immunobiology and pathogenesis of alpha chain disease Ciba found symp 4G: 1396, 1968.

16- Eeligmann M et al: Immunochemical stadies in four cases of alpha chain disease. J Clin Invest 48: 2374, 1969.

17- Seligmann M, Rambaud JC: Alpha chain disease. A possible model of the pathogenes of human lymphomas. comperhensive immunology, vol.9, eds J. Twomy RA Good New York, Planam Medical Book Company 1978, 425.

18- WHO Report: Alpha chain disease and related small intestinal lymphoma amemorandum. Bull WHO 54: 615. 1976.

19- Bognel JC et al: Stude elinique. anayomopathologique et immunoclinicalinque d'un nouveau cas de maladie des chains alpha suivi pendant. Cing ans. Rev Nur Etul Clin Biol 14, 362, 1972.

20- Rambaud JC et al: Non-searotory alpha-chain disease in intestinal lymphoma (Letter) N.Engl. J Med 303:53 1980.

21- Ali Khojasteh et al: Immunoprolifrative small intestinal disease. The New England Joernal of medicine Vol. 303, No. 23. June 9. 1983.

22- Annie Galian et al: Pathological study of alpha chains disease with special emphacis on evolution Cancer Vol, 69 May. 1977.

23- Z: Al Bahrani, T et al; Alpha heavy chain disease (report of 13 cases from Iraq) Gut, 1978, 19, 627-631).

24- Seligmann M et al: Alpha chain disease: A new immunoglobulin abnormality science 162: 1396, 1968.

25- Ramboud J C, Seligmann, M: Alpha chain disease. Clin Gastroenterol 3: 341 1976.

26- Seligmann M et al: Heavy Chain disease: Current findings and concepts. Immunol Rev. 48: 145, 1979.

27- Ramot B. et al: the mutual clonal origin of the lymphoplasmocytic an lymphoma cell in alpha heavy chain disease. Clin Exp: Immunol 27: 440, 1977.

28- Novis BH. Primary intestinal lymphoma in south Africa. Isr J Med Sei 1979: 15: 396-9.

29- Al Saleem TI. Evidence of acquired immune deficien-

ces in mediterranean lymphoma. a possible etiological lik. Lancet 1978, 2: 709-12.

30- Ramot B, Streiffer S. Raised serum-alkaline-phosphatase. Lancet 1966; 2: 587.

31- Guardia, J, Mirada. Morages Annengol JR. Martine 2-vazquez JM. Alpha Chain disease of the stomach. Hepatogastroenterology. 1980 27: 2389.

32- Rhodes JM, Teweil DP. Janossy G. Alpha-chain disease diagnosed by rectal biopsyden Br.Med.J. 1980.280-1043-4.

33- Gafter u.Kesler E, Shnabtary F, Shaked P,D Jaldetti M. Annormal chromosomal marker (D 149+) in a patient with alpha heavy chain disease. J. Clin Pathol 1980; 33: 136-44.

34- Savilahti F., Brandtzaog P.Kuitunen P. Atypical intestinal alpha chain disease evolving in the selective Immunoglobulin deficiency in a finnish boy.Gastroenterology 1980, 79: 1303-10.

35- Ramboud J.C. et al. Diffuse follicular Lymphoid hyperplasia of the small intestinal without primary immunoglobulin deficiency. Am J Med 1982; 73: 125-32.

36- Ceasal M, Duts H, Kehout E, Rezvani L. Immunoproliferative small intestinal disease with duodenojejunal lymphoma: Radologie changes, JR 1980: 135: 491-7.

37- Rambaud J. C Small intestinal Lymphoma and Alph-Chain disease Clinics in gastroenterology-Volume 12, No 3, September 1983.

38- Nikbin, B. Banisadre. M. Ala. F. and Mojtabai A. HLA awing, B_{12} immunoproliferative small intestinal disease-Gut. 20L 226. 1976.

39- Ament, M.E. and Rubin, C.E. Relation of Giardiasis to Abnormal intestinal structure and function in

Gastro Intestinal Immun Deficeincy syndormes. Gastro Entrology. 62: 216. 1972.

40- Bakhshandeh. K, Nasr, K, Haghighi P, and Hagshenas, M.: Glubbing and osteo Arthropathy Associated with primery upper small intestinal Lymphema J. Trop.Dis. Med. Hyg. 117 May 1971.

41- Banihashemi, A., Kohout, E., Dutz, W., and Rafii, R.: Abdominal Lymphoma and abnormal proteins-alpha heavy chain disease in Iran. Pahlavi. Med., J.4: 377,1973.

42- Hagshenas. M, Haghighi. P. Abadip, P, Kharazmi. A. Gerami; C. Nasr. K., Alpha heavy chain disease in souther Iran. Am. J. Dig. Dis. 22.866 1977.

43- Kamath, K.R. and Murugasu, A comparative study of four methods for detecting-Giardia Lamblia in children with diarrhea disease and malabsorption Gastroenterology 66: 16, 1974.

44- Nasr, K., Haghighi, p., Bakhshandeh, K., Abadi,P. and Lahimgarzadeh, A.: Primary upper small intestimal lymphoma : A report of 40 cases from Iran. Dig. Dis. 21: 313, 1976.