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Case Report

Immunoproliferative Small Intestinal Disease with 40-years of follow-up: A case of cured α-chain disease with recurrent lymphoplasmacytic tumors of the small intestine (MALT lymphomas)

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SUMMARY

Background: Immunoproliferative small intestinal disease (IPSID) represents a spectrum of clinicopathological entities including alpha-chain disease (α-CD) and other types of lymphoplasmacytic proliferations of the lamina propria of the small intestine, presenting with severe malabsorption. The disease may progress from a low grade MALT B-cell lymphoma to a high grade immunoblastic lymhoma.We present here a case of α-CD with an unusual evolution and long survival. Case - report: A 27 years old Greek man developed in 1967 severe diarrhea, abdominal pain and loss of weight. The diarrhea responded to treatment with antibiotics temporarily. His symptoms fluctuated and in 1971 the diagnosis of alpha chain disease was made. Treatment with cyclophosphamide and antibiotics until June of 1972 was followed by complete clinical recovery, return of histological appearances of the small intestine to normal and disappearance of the alpha chain proteins from the serum. He was symptom free without additional treatment until January of 1974 when he developed an ileocaecal tumor which was surgically resected. Histological examination concluded that it was a plasmacytoma consisting of 68% α cells and 15% λ cells. The patient had a course of radiotherapy and was put on maintenance treatment with cyclophosphamide. In 1977 he developed another tumour of the terminal ileum which was also resected. Histologically it was characterized as B-cell immunocytoma. He was treated with cyclophosphamide for 12 months. In December 1978 he developed again symptoms of abdominal neoplasm. At operation an inoperable tumour involving the small intestine and the mesenteric lymph nodes was found. Histological examination characterized it as a B-cell immunocytoma. He was treated with a monthly scheme of COP for two years (1979-1981) with success. Since then he is in perfect physical condition. Conclusion: According to recent studies this exceptional case, in retrospect, may be characterized as a cured case of α-CD with reccurent low grade MALT lymphomas of the small intestine showing extensive plasmacytic differentiation. The patient has been in perfect health for the past 26 years. Recent thorough investigation including immunological and molecular studies showed no evidence of alpha-chain disease or lymphoma.

Key words: Immunoproliferative small intestinal disease, MALT lymphoma, plasmacytoma, α-chain disease

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INTRODUCTION

The term 'immunoproliferative small intestinal disease' (IPSID) has been proposed by a WHO committee in 1976[1] to include cases of Mediterranean lymphoma[2,3] and alpha chain disease (α-CD),[4-6] that have common epidemiological, histopathological and immunopathlogical features. IPSID is now considered as a rare subtype of mucosa associated lymphoid tissue (MALT) lymphoma as has been originally defined by Isaacson[7] and in a recent WHO classification of

haematological malignancies is listed as a special variant of extranodal marginal zone B-cell (MALT) lymphoma.[8]

MALT lymphomas arise in lymphoid tissue following chronic antigenic stimulation mainly due to persistent infection as exemplified by Helicobacter *pylori* (*Hp*) infection in cases of gastric lymphoma.[9,10] The postulated cell of origin of MALT lymphoma is the marginal zone B-cell, which corresponds to a post germinal-centre B-cell, with rearranged and mutated immunoglobulin heavy and light chain genes.[11,12]

The term IPSID includes cases of classical α-CD,[4-6] of non-secretory α-CD[13,14] and cases producing other monoclonal immunoglobulins[15-17] free light chains[18,19] or polyclonal IgA[20-22] as all these cases have the same histopathological lesions irrespective of the type of immunoglobulin the proliferative lymphoid tissue cells may synthesize.[23] Galian et al[24] has proposed a histopathological classification and staging for cases of α-CD that may be applied to all IPSID cases.

The histological features of IPSID are those of a low-grade B-cell lymphoma of MALT with marked plasma cell differentiation. In stage A the lymphoplasmacytic infiltrate is confined to the mucosa and the mesenteric lymph nodes. In stage B it extends below the muscularis mucosae. This stage is characterized by the presence of aggregates of centrocyte-like B cells that cluster around epithelial crypts forming lymphoepithelial lesions. A characteristic immunophenotype feature of these cells is the CD20 positivity.[11,25] In some cases lymphoid nodules are formed that may lead to the so-called follicular lymphoma variant. In stage C the development of lymphomatous masses and transformation to a high-grade lymphoma is observed.

Rare cases of IPSID have been shown to respond to broad spectrum antibiotics.[26,27] Smith *et al*[28] using molecular techniques for the analysis of DNA from mucosal tissue, identified the presence of monoclonal lymphoid populations in stage A when the lymphoplasmacytic infiltrate is still responsive to antibiotics thus suggesting a malignant process even in cases initially appearing as benign.[29,30]

We present here a patient with a 40 year follow-up who achieved a complete cure of α-chain disease but subsequently the patient developed reccurring intestinal MALT lymphomas with extreme plasmacytic infiltration which eventually responded to cytotoxic treatment. A recent reevaluation confirmed that he is still disease free and is now considered as cured.

METHODS

We used a variety of biochemical, haematological immunological histological, molecular, endoscopic and imaging techniques to study this patient during the course of his disease. Serological methods included electrophoresis, immunoelectrophoresis and the measurement of serum immunoglobulins with standard techniques. For the detection of free alpha-chain protein in blood, concentrated urine and jejunal fluid the immunoselection plates, as described by Doe *et al*.,[34] were used. Peroral biopsies of the small intestine were also taken, as well as multiple biopsies from the gut and lymph nodes during surgery. Sections were stained for detection of cytoplasmic Igs using the immunoperoxidase technique.[35] A quantitative estimate of the number of plasma cells stained for each immunoglobulin class and κ, λ light chains in the lamina propria and mesenteric lymph nodes was made using a point-counting method described by Skinner and Whitehead.[36] Staging of the patient was based on the histopathological classification of Galian et al.[24]

Immunophenotyping of lymphocyte subsets was made by flow cytometry in whole blood samples by direct, double or triple immunofluorescence using a panel of monoclonal antibodies (mAbs) of Becton Dickinson and a FACS scan / FACS Caliber cytometer. Lymphocyte proliferation responses to phytohaemaglutinin (PHA) and to costimulation with CD3+CD28 mAbs were carried-out in whole blood cultures[37,38] The method in detail is described elsewhere.[39] Investigation for the presence of various autoantibodies and Hp antibodies was made using standard techniques.

Examination of bioptic material during reevaluation in 2005

The study was done on bioptic material taken from duodenum, gastric antrum, small and large intestine. Biopsies were formalin-fixed and paraffin embedded and stained with H&E for routine microscopy. Ten, 3μm consecutive sections from each specimen were placed on + charged slides (Superfrost) and proceeded to immunohistochemistry (HIC) and molecular analysis including fluorescence *in situ* hybridization (FISH) and chromogenic *in situ* hybridization (CISH) assays. A cohort of monoclonal antibodies against IgA, IgG, and IgM heavy chains as well as for κ and λ light chains, were selected for this study. All the antibodies were provided by DAKO, Denmark and Biogenex, USA. Chromosomal abnormalities concerning chromosomes 14, 2 and 22 were determined using the appropriate probes; CISH spot light (chromogenic ISH Detection Kit-Zymed) was applied.[40,41] Analysis of transloca-

tion t(11;18), t(9;14) and t(5;19) was done by FISH probes provided by Vysis Abbott USA and known protocol.[42]

CASE REPORT

The patient was a 27-year-old Greek waiter born in a very poor village of Thessaly, who developed diarrhoea in 1967. Stool examination revealed the presence of giardiasis, and a course of mepacrine therapy produced only temporary improvement.

1970-1971

In April 1970 he was admitted to hospital, where he was found to be emaciated, with ankle oedema and appreciable finger clubbing. At that time heamoglobin, WBC count, ESR, and bone marrow were normal, but serum albumin (2.6g/dl) and potassium (2.8mmol/L) were low. There was malabsorption of D-xylose, (only 2.5 g of a 25-g oral loading dose being excreted in the urine) and of B_{12}. Faecal fat was appreciably increased (44 g/24hr, normal <5g). The results of stool examination were repeatedly negative for ova, cysts and parasites.

Barium follow-through of the small bowel was abnormal with dilated loops coarse mucosal folds, and diffuse nodular appearance. The jejunal biopsy showed considerable reduction in villous height, a well preserved epithelium, crypt sparsity, and a very dense cellular infiltrate of the lamina propria, consisting mainly of lymphoid cells and plasma cells (Fig 1). A large bowel biopsy showed diffuse infiltration of the mucosa and submucosa with plasma cells.

Serum immunoglobulin estimations showed severe hypogammaglobulinaemia especially affecting the IgG and IgM classes (IgG: 190mg, IgM: 14mg and IgA: 66mg/dl) (Table 1). There was a deficient antibody response after immunization with TAB, but lymphocyte responses to stimulation by phytohaemaglutinin (70% blast transformation) and purified protein derivative (6% blast transformation) were normal.

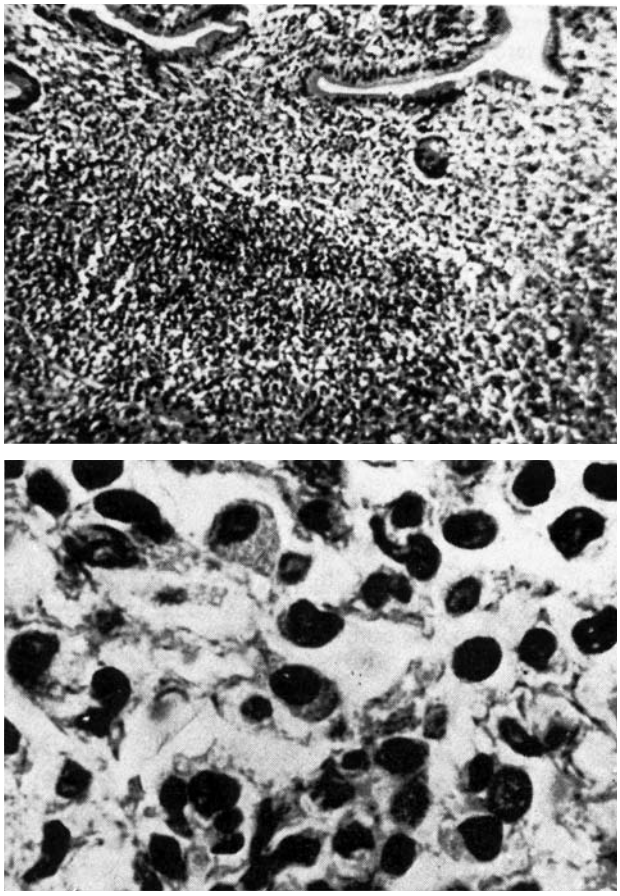

Figure 1. Peroral small intestinal biopsy taken in 1971. The histological examination shows atrophy of villi, dense lymphoplasmatic infiltration and sparsity of crypts.

There was no response to a gluten-free diet over a two month period, and because of the hypogammaglobulinaemia and diarrhoea, oral tetracycline (1g/d) was given. There was a striking but temporary symptomatic improvement and his weight increased by 3Kg. Subsequently, non-absorbable sulphonamides (3 g/d) and oral prednizolone (15mg/d) were given for six weeks.

In March 1971 there was a rapid deterioration of the patient's condition, who appeared emaciated. Abdominal pain,

Table 1. Serum immunoglobulins during the evolution of the disease

	1970-1971	1974-1976	1977	1982-1990	2005
IgG (mg/dl)	120-310	750-1500	970	790-1080	1230
IgA (mg/dl)	66-103	78-108	85	66-112	141
IgM (mg/dl)	14-21	63-128	66	66-125	54
α-heavy chains	positive	negative	negative	negative	negative
kappa light chains (mg/dl)					214
lamda light chains (mg/dl)					136

and diarrhoea increased and polyuria and vomiting were aided. The main laboratory findings were low serum potassium (2.2 mmol/l) and albumin (2.9 g/dl) and abnormal absorption tests (D-xylose excretion= 2.2 g of a 25 g oral dose and feacal fat: 21.4 g/24h). A second jejunal biopsy specimen confirmed the previous findings. The cellular infiltrate consisted predominantly of plasma cells with a significant proportion of cells intermediate in type between lymphocytes and plasma cells. These findings were suggestive of α-chain disease, stage A. This diagnosis was subsequently confirmed with the immunoselection plate technique.

Initially intravenous cyclophosphamide (100-200 mg daily) was given together with a five-day course of prednisone (60 mg daily) One month later his clinical condition improved markedly and his body weight had increased by 3 Kg. However the polyuria persisted, it was attributed to hypokalemic nephropathy and the patient was treated with intensive replacement potassium therapy. In May 1971 some diarrhoea persisted but after the addition of tetracycline to oral cyclophosphamide therapy, he further improved and his diarrhoea ceased. He rapidly gained weight (23Kg over 3 months) and his finger clubbing disappeared. Over the next 10 months oral cyclophosphamide 100 mg/d and intermittent oral antibiotic therapy were continued.

1972-1973

In June 1972, 15 months after diagnosis of alpha-chain disease, all treatment was stopped. The patient was symptom free and was able to resume full-time employment. A peroral jejunal biopsy taken in February 1973 showed villi of normal height and normal cell population in the lamina propria (Fig 2). The immunological abnormalities also completely regressed. Normal IgA-producing cells were now shown in the small intestinal mucosa by immunofluorescence and serum and urine alpha chains were absent. Complete remission was still maintained in December 1973, 18 months after all treatment ended.

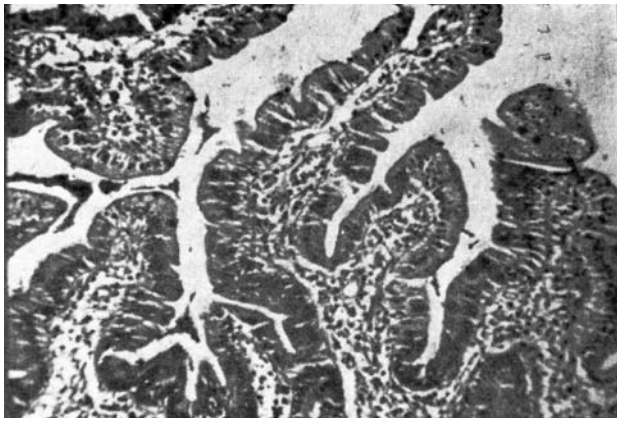

Figure 2. Peroral small intestinal biopsy taken in 1973 shows villi of normal hight and normal cellularity of the mucosa.

1974

In January 1974 the patient developed persistent abdominal pain located in the right ileal fossa. A hard tender mass in the same area was palpable. Barium studies showed a lesion involving the terminal ileum and the caecum (Fig 4). A peroral jejunal biopsy was essentially normal. D-xylose excretion was normal but faecal fat was elevated (16.5g/24h). At laparatomy a tumour involving 7 cm of the terminal ileum and 6 cm of the caecum was found and completely resected. The histological findings (dense infiltration of all layers of the bowel wall by mature plasma cells with the accumulation in some areas of lymphocytes and hitiocytes) were consistent with a diagnosis of "plasmacytoma". The immunoperoxidase study of the sections and the quantitation of immunoglobulin containing cells showed that in the "normal" area of the small bowel the counts did not differ from the normal controls with respect to γ, α, and μ staining cells; in the tumour margin there was a moderate increase of α and λ cells whereas in the tumour there was a significant increase in α cells together with an excess in λ cells (52) (Table 2). The patient had a

Table 2. Immunoperoxidase study of the small bowel biopsy in 1974. Number of α, γ, μ, κ, and λ staining cells per unit volume of the lamina propria of the patient's normal bowel, tumour margin, the tumour and normal controls.

Cells/1000 pts lamina propria				
		Patient		
Immunoglobulin class	**Controls (Mean+/-SD)**	**"Normal" small bowel**	**Tumour margin**	**Ileal tumour**
IgA	1050+/-350	1810	4500	8600
IgG	150+/-45	190	6000	67
IgM	230+/-50	280	1800	occ. cell
κ	810+/-200	1315	5985	occ. cel
λ	720+/-150	1035	7315	1896

(From Skinner et al 1976)

course of radiotherapy and was then put on maintenance treatment with cyclophosphamide.

1977-1978

The patient was well until October 1977 when a new localized tumor of the terminal ileum was diagnozed and surgically resected. Histologically it was composed of lymphoid cells with increased numbers of plasma cells (over 50%) with a few more immature forms and immunoblasts and was characterized as a "B-cell immunocytoma". The excised mesenteric lymph nodes had normal architecture and cellularity. Serum immunoglobulins were within normal limits and no alpha heavy chains were detectable (Table 1). Treatment with cyclophosphamide was reinstituted. In November 1978 while on treatment with cyclophosphamide he developed an abdominal mass which was shown at operation to be an unresectable massive tumour of mesenteric lymph nodes. The histological examination showed partial desorganization of lymph node architecture. The cell infiltrate consisted of diffuse proliferation of small lymphocytes, plasmacytoid lymphocytes and plasma cells (Fig 3 and 4). The growth pattern was interfollicular. The lesion was again characterized as non Hodgkin's lymphoma of the type of B-cell immunocytoma. The immunoperoxidase staining of the lymph node sections showed a polyclonal cytoplasmic immunoglobulin pattern with increased numbers of α, γ, μ, κ and λ chains and a slight excess of λ to κ chains (ratio 1.5:1.0) (Table 3).

During all this period serum and urine examination for free alpha chains was negative and serum immunoglobulin levels were normal (Table 1). The patient responded to courses of cyclophosphamide, oncovin and prednizolone given over a period of 2 years and he remains disease free and in good health since then having a survival of 40 years since the onset of his symptoms. During all these years the disease histopathology did not progress beyond Galian stage B. A summary of the patient's clinical symptoms and findings and treatment modalities is shown in table 4.

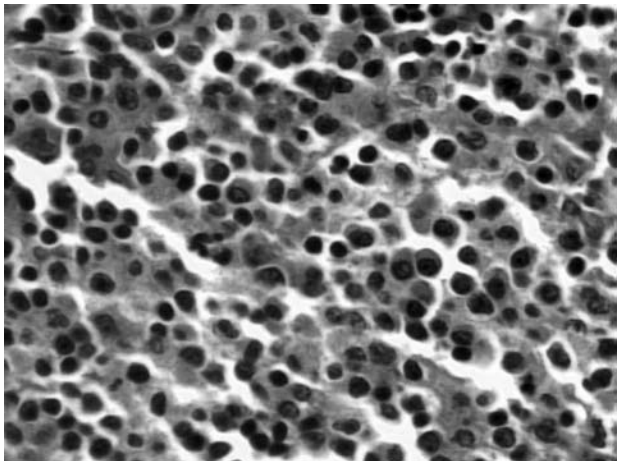

Figure 3. Biopsy of the tumour developed in 1974 showing dense infiltration with real actively mature plasma cells. Staining for IgA with the immunoperoxidase technique.

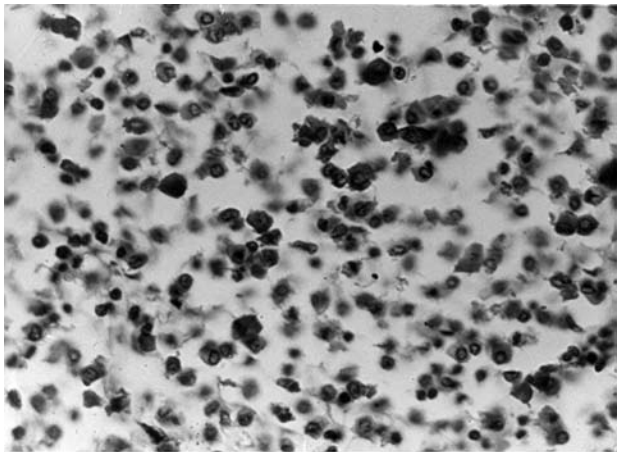

Figure 4. Cell morphology of the tumour developed in 1978 consisting mainly of plasmacytes lymphocytes and plasma cells.

2005

In 2005 he had a complete clinical and laboratory reevaluation with the following investigations and results:

Table 3. Immunoperoxidase study of the small bowel and lymph node biopsy in 1978. Numbers of α, γ, μ, κ, λ, staining cells per unit volume of patient's biopsy and of normal controls (mean values +/- 1SD).

	Cells / 1000 pts			
	Jejunum		Mesenteric lymph nodes	
Immunoglobulin class	**Patient**	**Controls**	**Patient (tumor)**	**Controls**
IgA	110	249 +/- 70	1062	161 +/- 75
IgG	10	36 +/- 21	827	95 +/- 41
IgM	36	60 +/- 22	102	44 +/- 25
κ	80	192 +/- 46	1027	166 +/- 45
λ	117	124 +/- 37	1511	36 +/- 21
ratio λ:κ	1.4:1.0	0.6:1.0	1.5:1.0	0.2:1.0

Table 4. Case report summary

1967	Onset of symptoms (diarrhoea, loss of weight, abdominal pain)
1971 (March)	Diagnosis of α-chain disease. Stage A. (Cyclophosphamide for 15 months)
1972-1973	Complete clinical and histological remission
1974 (January)	First localised plasmacytoma of terminal ileum and caecum (Stage B). Lymph nodes (Stage A). Complete resection, radiotherapy and intermittent cyclophosphamide.
1977 (October)	Second localised immunocytoma of terminal ileum. Complete resection (Stage B). Lymph nodes (Stage A). Cyclophosphamide (1g/mox12mo).
1978 (November)	Extensive involvement of mesenteric lymph nodes. Unresectable mass at laparatomy. Histological examination shows partial obliteration of architecture and a dense infiltrate composed of centrocytes, plasmatocytoid cells, plasma cells, and a few immunoblasts and polyploidy cells (Stage B).
1979-1980	Combination therapy with courses of: Alkeran 15mgX5 days, Oncovin 2mg, Prednisolone 100mg X 5 days at monthly intervals. for two years. Clinical remission
1981-1989	Regular clinical and laboratory examination shows complete remission without any additional treatment. Steady body weight 72-74 Kg. CT Scan of the whole abdomen (years 1982, 1983, 1989): normal. Serum immunoglobulin pattern: normal.
2005	On reevaluation, clinical, immunological and molecular examination confirms complete cure

Biochemical and haematological profile

Normal.

Protein studies

Electrophoresis and immunofixation of serum proteins showed no abnormality. Serum immunoglobulin estimation showed values within normal limits (Table 1). Immunoselection plate was negative for free alpha chains in serum. Complement components C3, C4 were within normal range.

Autoantibodies

Anti-nuclear, anti-DNA, anti-endomysial anti-gliadin IgG and IgA and anti-tTG antibodies were negative. Serum antibodies for Helicobacter *pylori* were positive as follows: IgG>150 NTU/ml (positive>20), IgA:49 NTU/ml (positive>20).

Immunophenotyping of peripheral blood lymphocyte subsets with flow cytometry

The analysis showed a moderate decrease of the percentage of CD4+ T-cells and an increase of natural killer cells (Table 5).

Lymphocyte functional tests

Lymphocyte proliferation responses to PHA and to anti-CD3+anti-CD28 costimulation were within normal limits (Table 6).

Examination of bioptic material: The biopsies taken from duodenum and the small and large bowel showed no exceptional pathologic findings. Few scattered plasma cells were observed in the lamina propria but the number was within normal limits. Biopsies taken from gastric antrum revealed a mild-to-moderate Helicobacter pylori gastritis with mild atrophic changes.

Table 5. Lymphocyte subsets (percent of total lymphocytes)

Surface markers					
T-cells		**B-cells**		**Other markers**	
CD2	76	CD19	16	HLA-DR	36
CD3	58	CD20	16	CD23	10
CD4	31	CD22	21	CD38	17
CD5	59	FMC-7	15	CD57	19
CD7	68	κ	10	CD138	0
CD8	28	λ	6	CD3-CD16/56+	20
CD7+HLA-DR+	17	CD5+ CD19+	1	CD3+ CD/6/56+	2
CD57+ CD8+	13	CD20+ CD23+	10	CD38+ CD138+	0
		CD38+ CD22+	8		
		FMC-7+ CD11c+	3		

Table 6. Lymphocyte proliferation responses

Stimulation	Counts per minute	Stimulation index (SI)
Without stimulation	1175	
Anti-CD3+ anti-CD28	161,265	138
PHA	31,507	28

In normal responses SI>5

Immunohistochemistry: No evidence of monoclonality either of heavy or light chains in small and large bowel specimens was revealed and a polyclonal pattern of heavy and light chains expression was noticed.

Molecular methods (FISH and CISH analysis): No evidence of t(11;18), t(9;14) and t(5;19) translocations was found on tissue samples examined by FISH. Moreover, no extra sign of diploidy and/or polysomy concerning chromosomes 14, 2 and 22 was showed by CISH method.

DISCUSSION

The patient under discussion, a Greek man born in a very poor village in Thessaly developed severe diarrhoea and signs of malabsorption at the age of 27 years, in 1967. In 1971 he was diagnosed as a case of alpha chain disease and was followed up till today (40 years).

The two main characteristics of the case were: a) the complete and long lasting disappearance of symptoms, signs, and laboratory evidence of alpha chain disease after treatment with cyclophosphamide and broad spectrum antibiotics. b) The fact that despite the lack of activity of α-CD small intestinal tumors heavily infiltrated by plasma cells developed and relapsed after surgical excision and treatment with radiotherpay and cyclophosphamide.

The first tumour at the terminal ileum and caecum had been characterized as an extramedulary plasmacytoma in keeping with a definition proposed by Rappaport.[45] The second tumor also involving the ileum was characterized as B-cell immunocytoma according to the Kiel clasification. The third tumour, probably originating from the small bowel, eventually involved the mesenteric lymph nodes and because it was inoperable the patient was treated with a combination of chemotherapeutic agents (COP) for two years. This tumour was again characterized as B-cell immunocytoma. Since then and for the past 26 years the patient is in good health and leads a normal life.

In the early 1980's important new findings by Isaacson and colleagues gave rise to the novel idea that the intestinal lymphoplasmacytic infiltrate of IPSID is a MALT lymphoma[7] and more precisely it represents an "extranodal marginal zone (MZ) B cell lymphoma of mucosa associated lymphoid tissue".[11] MZ B-cells are thought to capture, process, and present antigens and to deliver co-stimulatory signals to T cells. In addition these cells display the capacity to differentiate into plasma cells. In keeping with this hypothesis, MALT lymphomas often include high numbers of plasma cells, a phenomenon termed plasmacytic differentiation. According to Woehrer et al[46] this feature is especially prominent in IPSID and it may explain cases initially described as extramedullary plasmacytomas within classical MALT organs such as the G.I. tract,[47,48] which might in fact be MALT lymphomas with extensive plasmacytic differentiation. Extramedullary plasmacytomas result from B-cells that develop in and home back to the MALT system – These tumors contain reactive follicles, lymphoepithelial lesions, centrocyte like cells and monocytoid B cells together with large numbers of plasma cells ranging from 55% to 90% of the lymphoid cells, thus having many features of marginal zone lymphomas.[49,50] A recently reported case of primary gastric plasmacytoma that had a complete regression following *Hp* eradication by antibiotic therapy[51] has been discussed as an example of disguized MALT lymphoma.[52] It is interesting that our case appears to be a further example along these lines of thinking. The first localized tumor of the patient (1974) in the ileocaecal area was characterized as plasmacytoma as there was dense infiltration of all layers of the bowel by plasma cells. The second (1977) and the third (1978) subsequent tumours that at the time they had been characterized as B-cell immunocytomas they had areas of intense plasmacytic infiltration containing also centrocytes, few immature cells, and immunoblasts. Using the current terminology all these tumors could be described as MALT lymphomas.

The quantitative immunohistochemical studies have produced interesting findings. The first tumour developed in 1974 was found to contain 68% α and 15% λ cells. The excess of α-chains in relation to λ chains suggested that the tumor contained two clones of plasma cells; one producing only α-chains and the other monoclonal IgAλ or free λ-chains. The fact that no free alpha chains were detected in the serum may be explained in several ways: a) the abnormal plasma cells were not secreting their immunoglobulin product; b) the tumour mass was not extensive enough to produce a detectable amount of α-chains in the serum. The finding that the bowel distant to the tumor was histologically normal and had a normal pattern of immunoglobulin producing cells supported the view that the initial α-chain process of the patient was still in remission and that the development of the "plasmacytoma" represented a local growth probably from a different cell clone.

Table 7. History of infection (percent incidence) and serum IgA levels (mg/dl) in a sample of Athens' and Thessaly's population.

Subjects	Number	Diarrhea	Salmonelosis	Brucelosis	HBsAg	IgA
Rural pop	390	7.2	6.7	5.4	5.9	200
Urban Pop	204	0.5	1.5	0.0	0.5	182

Manousos et al 1978 (59)

The third tumour developed in 1978 showed to consist of cells with a polyclonal immunoglobulin pattern but again an excess of λ to κ chains was observed. The clonal relationship of these tumours to the original α-chain disease of the patient that had completely regressed is uncertain as we have no data from a molecular analysis. In most cases immunohistochemical studies have failed to show light chains in α-chain disease. However, Isaacson and Pride[18] have described two cases of α-CD in which immunohistochemistry disclosed the presence of monotypic light chains that correlated with the α positive plasma cells. These authors believe that the disordered immunoglobulin synthesis leads to loss of light chains which may persist to some degree in plasma cells and consider that the α1 heavy chains and the light chains originate from the same clone in these particular cases.

The etiopathogenesis of these tumors is also obscure. Guardia et al[53] have reported on the evolution of a patient with α-CD who after a 28 months complete remission following treatment with CP, prednizolone and doxycycline developed a retroperitoneal immunoblastic lymphoma associated with G-kappa paraproteinemia while the intestinal biopsy was normal. Woehrer et al[46] discuss another case of MALT lymphoma involving the stomach and the lung that, following treatment with the anti-CD20 monoclonal antibody rituximab and a partial remission of the lymphoma, developed a pure plasma cell tumor that was negative for CD20 and showed kappa-light chain restriction. These examples suggest that after eradication of the intitial neoplastic lymphoma cells, following cytotoxic treatments, an overgrowth of some of the plasmacellular components of the MALT lymphoma may take place.

The case we report here is remarkable because of the recurrent MALT lymphomas occurred observed within a period of 5 years following remission of α-CD that were eventually completely cured as a result of a longstanding treatment with COP.

IPSID, like gastric MALT lymphomas, appears to have an infectious etiology[10,54] and there is sufficient evidence that clonal cell expansion is the result of chronic antigenic stimulation.[12]Thus IPSID has recently been added to the growing list of infectious pathogen associated lymphomas. Clinical, immunohistochemical and molecular studies have demonstrated an association with H. *pylori*[55,56]more significantly with Campylobacter jejuni.[57]

The patient under discussion originated from a poor rural area of Thessaly. It was interesting that another of our early cases of IPSID was born and raised also in the same area.[58]In view of this occurrence we had made an epidemiological investigation in this area and studied the serum immunoglobulins in samples from the rural population of Thessaly and from the urban population of Athens.[59] The results showed an increased incidence of episodes of diarrhoea and other infections in the rural population and significantly higher levels of serum IgA (Table 7). Moreover in this rural population of 390 subjects two cases of monoclonal gammopathy (IgA-λ and IgG-λ) were identified together with two cases of selective IgA deficiency. This incidence is higher than that expected in the general population. These findings indicate the significance of infectious agents in the case of our patient. Also the recent finding of the presence of *Hp* infection and of detectable specific histopathologic lesions in the stomach may suggest that Hp may be another contributing factor.

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