IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE

(IPSID); a model for mature B-cell neoplasms.

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Abstract

Immunoproliferative small intestinal disease (IPSID) was recently added to the growing list of infectious pathogen-associated human lymphomas. Molecular and immunohistochemical studies demonstrated an association with Campylobacter jejuni. IPSID is a variant of the B-cell lymphoma of mucosa associated lymphoid tissue (MALT), which involves mainly the proximal small intestine resulting in malabsorption, diarrhea and abdominal pain. Geographically, IPSID is most prevalent in the Middle East and Africa. IPSID lymphomas reveal excessive plasma cell differentiation and produce truncated α heavy chain proteins lacking the light chains as well as the first constant domain. The corresponding mRNA lacks the V_H and the C_H1 sequences and contains deletions as well as insertions of unknown origin. The encoding gene sequence reveals a deletion of V region and parts of C_H1 domain. Cytogenetic studies demonstrated clonal rearrangements involving predominantly the heavy and light chain genes, including t9;14 translocation involving the PAX5 gene. Early stage IPSID responds to antibiotics (30-70% complete remission). Most untreated IPSID patients progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall, mesenteric lymph nodes, and may metastasize to a distant organ. IPSID lymphoma shares clinical, morphological and molecular features with MALT lymphoma, lymphoplasmacytic lymphoma and with plasma cell neoplasms.
Introduction

Malignant lymphomas of the small intestine are relatively common in certain geographic areas and they seem to be particularly so in developing countries, especially in the Middle East and North Africa.\(^1\) In the Iraqi tumor registry (1986-1988), for example, small intestinal lymphoma constituted about 19% of all non-Hodgkin lymphomas and 78% of all small intestinal malignant tumors. Generally, these lymphomas can be divided into three subtypes.\(^2\) Burkitt lymphoma, which is most common in children, usually involves the terminal ileum with extensive abdominal involvement. The second, relatively uncommon, is similar to the “Western” type of non-Hodgkin lymphomas most commonly large B-cell type involving various parts of the small intestine. The third type is the so-called Mediterranean lymphoma affecting mainly young adults with almost equal sex incidence and involves predominantly the proximal small intestine and is usually associated with chronic diarrhea and abdominal pain.\(^3\) In 1978, the World Health Organization recommended the term “Immunoproliferative Small Intestinal Disease (IPSID)” for the syndrome associated with Mediterranean lymphoma because at that time it was felt that the disease in its early stages “does not appear to be truly malignant lymphoma”.\(^4\)

Many of the patients with IPSID syndrome were found to have variable levels of abnormal immunoglobulin in the serum or other body fluids, which was later identified to be truncated α heavy chains (αHC).\(^5\) Generally, at the present time IPSID is considered as a variant of mucosa associated lymphoid tissue (MALT) lymphoma.\(^6\) In the recent
WHO classification of hemopoietic and lymphoid tissue IPSID is listed with the heavy chain diseases as a special variant of extranodal marginal zone B-cell (MALT) lymphoma. However, the WHO classification does not recognize the so-called “non-secretory” IPSID as a specific entity. This variant, similar to MALT lymphomas of other mucosal sites is characterized morphologically by the proliferation of small centrocyte-like lymphoid cells lacking the extreme plasmacytic differentiation observed in αHC secretory form. Both “secretory” and “non-secretory” forms are common in the same geographic area, but have different local geographic distribution. For the purpose of this review, the terms IPSID and α heavy chain disease (αHCD) are used synonymously to refer to the secretory form, a relatively well defined clinicopathologic entity. This is notwithstanding the fact that there are rare patients with γ rather than α heavy chain IPSID and the rare colonic, gastric or pulmonary αHCD. IPSID is a unique mature B-cell neoplasm regarding its epidemiology, clinical features, morphology and molecular pathogenesis. It shares certain features with gastrointestinal MALT lymphomas, lymphoplasmacytic lymphoma as well as plasma cell neoplasms. Though rare in many parts of the world, clinical experience and molecular investigation over the period of four decades has contributed not only to the diagnosis and management of IPSID, but also to the understanding of the pathogenesis and evolution of these B-cell neoplasms.

**Epidemiology and clinical features**

IPSID affects mainly older children and young adults (10-35 years old, mean 25-30), of low socioeconomic status in developing countries. It is uncommon in young children and older adults. Geographically, the majority of cases reported were from the Middle East, North and South Africa, and the Far East. Sporadic cases have been
reported from other countries and continents, especially in immigrants from the Middle East and North Africa. Clinically, intermittent diarrhea and colicky abdominal pain are the most frequent symptoms. Other symptoms and signs are mainly related to malabsorption. Intestinal obstructions, abdominal masses and ascites are common in advanced stage (Table 2). The differential diagnosis usually includes chronic infections, parasitic infestations, sprue, tropical sprue and lymphomas other than IPSID. Although the clinical, laboratory and radiologic findings are pathognomonic, the final diagnosis is usually established by endoscopic biopsies and/or laparotomy. Upper gastrointestinal endoscopy shows abnormalities in the second, third and fourth parts of the duodenum and upper jejunum in all patients except very early in the disease. Thickening, erythema and nodularity of the mucosal folds are noted. As the disease progresses, tumors appear usually in the proximal small intestine and rarely in the stomach.

Pathology and Evolution:

The main pathological feature of IPSID is the presence of dense mucosal infiltrate of “centrocyte-like” and many plasma cells involving long segments of the small bowel mucosa, predominantly the proximal parts. The overlying epithelial cells are usually intact, and the crypts are sparse. Progression to higher grade large cell lymphoplasmacytic and immunoblastic lymphoma is characterized by increased plasmacytic atypia with the formation of aggregates and later sheets of dystrophic plasma cells and immunoblasts invading into the submucosa and the muscularis propria. This large cell component seems to evolve within the diffuse “low grade” IPSID and is clonally related to it. The rate of evolution of IPSID from low grade to
higher grade is not known. Most patients are diagnosed at the time of this transformation due to the severe symptoms of abdominal pain and obstruction. However, they usually have mild IPSID-related symptoms dating back up to five, or even ten years earlier. Patients with IPSID-associated large cell lymphomas are six years older than those with pure IPSID, a statistically significant difference. Hepatic, splenic or peripheral lymph node involvement are uncommon except in the late stages of disease. Bone marrow involvement and leukemic manifestations are rare.

**α heavy chain protein: diagnosis, structure, synthesis and secretion:**

The immunological hallmark of IPSID is the presence of anomalous α heavy chain protein in the serum detected in 20% to 90% of patients. The higher detection rate reflects recent improvement in immunologic technique, especially the use of immunoselection. Immunelectrophoresis into gel containing especially developed anti-Fab alpha serum provides the most sensitive and specific detection system for αHCD protein. Alternatively, immunoselection is performed in 1% agarose gel incorporated with 30% v/v antikappa and antilambda antisera. Upon immunoelectrophoresis normal IgA precipitates around the trough while αHC protein migrates freely toward the anode producing various abnormal precipitation lines. In our own experience in Iraq, this latter immunoselection technique detected αHC protein in 42% of patients with a clinicopathologic picture of IPSID. This ratio was much higher (about 70%) if the non-invasive low grade phase patients only are considered (Table 1). In some apparently αHC negative patients, the abnormality can be identified through
immunohistochemical or immunofluorescence staining of the small bowel biopsies. These stains demonstrate positivity for αHC, while the light chain stains are negative.

αHCD proteins are almost always α1 species and appear to consist largely of multiple polymers of different sizes. The molecular weight of the basic monomeric unit varies between 29,000 and 35,000. Allowance is usually made in these figures for carbohydrate, since the carbohydrate content of many of these αHCD proteins is unusually high. Thus, the length of the basic polypeptide subunit varies from patient to patient and in most instances it is between half and three-fourths the size of its normal counterpart. Sequenced data showed that the αHCD protein lacked the VH and the first constant domain. Normal sequence resumed at the beginning of the hinge region, with a valine residue corresponding to position 222 of a normal α1 chain. The carboxy terminal structure and conformational integrity remain intact.

As expected, the αHCD messengerRNA lacks the VH and CH1 sequences. It also contains an in-frame insert of unknown origin between the leader peptide and the normal CH2 and CH3 coding sequences. These inserts are of variable length (42 to 105bp) and they are unrelated to each other. Their structure suggests that they result from alternative splicing process. These sequences do not resemble any normal human genomic DNA. The absence of homology between these insertions could not support the hypothesis of infectious non-human DNA, either. They may represent highly altered sequences from human Ig locus. Since the amino acid sequence of αHCD proteins
begins with a C_H2 domain, it is most likely that the amino acid terminal sequence encoded by these insertions is cleaved intracellularly before secretion.\textsuperscript{36}

The complete gene sequence encoding three \( \alpha \)HCD proteins, MAL,\textsuperscript{35} YAO\textsuperscript{37} and SEC has been determined.\textsuperscript{38} These three genes show a striking similarity in their position and extent of the two main deletions, which encompass sequences in the V/J and the switch/C_H1 regions. In all cases, most, or all of the V region is deleted as is the sequence starting in the switch region and extending through part, or all of the C_H1 domain.\textsuperscript{39} These findings are also similar to those present in the two \( \gamma \) heavy chain proteins gene sequenced (OMN\textsuperscript{40} and RIV\textsuperscript{41}). Taken together the analysis of \( \gamma \) and \( \alpha \)HCD proteins and nucleic acids seem to show the emerging pattern of two large non-contiguous deletions in the heavy chain genes and the expression of low levels of light chain constant regions.\textsuperscript{40}

Analysis of the DNA from IPSID tumors showed monoclonal heavy and light chain gene rearrangement even in the early stages of the disease.\textsuperscript{42} Southern blot analysis established that in all cases one or both \( \kappa \) genes were rearranged in tumor DNA, whereas the \( \lambda \) genes were in germ-line configuration. In some cases, the truncated mRNA were shorter than a normal kappa mRNA. This finding was interpreted as indicating the occurrence of genomic alterations in both heavy and light chain loci in HCD, as demonstrated by the analysis of the sequence of rearranged \( \kappa \) gene in a case of \( \gamma \) HCD.\textsuperscript{43} As a characteristic of \( \alpha \) and \( \gamma \) HCD there are no light chains detected in the serum or associated with the heavy chain fragments in most cases. Studies reported from various laboratories suggested that independent structural gene abnormalities are at least partially responsible for the uniform absence of detectable light chain production in HCD. In contrast to most normal and neoplastic Ig-producing cells, there is excess of heavy to
light chain mRNA as well as protein. The elegant experiments by Teng, et al demonstrated that this excess is a function of the cell independent of structural gene abnormality and is due to a low level of light chain transcription. Transcription can be increased by fusing the HCD cell line to murine myeloma cell line or transfecting the defective light chain gene into a murine plasma cell. Other findings suggested that the examined HCD cells either lack a transcription factor present in mature plasma cells or have a functional repressor of light chain transcription.

The synthesis of αHCD protein by the proliferating cells has been demonstrated by immunofluorescence and/or immunohistochemical method and by biosynthesis studies. These studies and those of the membrane-bound Ig have shown that the immunoblastic cells in late stage disease do not synthesize αHCD protein. In all cases studied, the αHCD protein was found in the jejunal juice when it was already present in the serum. αHC protein was found in the intestinal or gastric lumen in some cases, although it was undetectable in the sera of these patients in spite of the use of the most sensitive technique. The concentration of αHCD protein in urine is low and Bence-Jones proteinuria has never been found. It was also noted that in rare cases the αHCD protein is absent from the serum, urine and jejunal juice, but can be demonstrated by immunohistochemical staining of small bowel biopsies or that the Ig gene is rearranged by molecular studies. It was demonstrated that gene deletions force “non-secretory” αHCD plasma cells to produce membrane form αchain only. In the vast majority of αHCD, however, secretion of truncated αHC could be demonstrated by various techniques.
Normal mammalian α chains are 50 kDa and contain one variable and three constant region domains. Plasma cells in mucosal tissue assemble polymeric IgA intracellularly from monomeric IgA. Normal plasma IgA is monomeric, while mucosal IgA is dimeric or tetrameric. It contains joining (J) chains that help recognize the receptor (pIgR) expressed on basolateral surfaces of adjacent epithelial cells. Light chains have been shown to play a critical role in the Ig molecule secretions by the plasma cells. In αHCD mutations in the both heavy and the light chains seem to result in the secretions of the truncated α heavy chains by the neoplastic plasma cells in spite of the absence of light chains. J-chains are present in the majority of αHCD proteins. However, the production of these truncated αHCD proteins probably outpace the synthesis of the secretory component by the enterocytes. This could be expected because in IPSID the crypts are atrophic and highly dispersed in contrast to celiac disease where they are hyperplastic. Thus, large amounts of polymeric αHCD protein can usually be demonstrated in the serum and also in the jejunal and gastric fluids.

**Cytogenetics of IPSID:**

Although considered as a variant of MALT lymphoma, IPSID lacks the (11;18) chromosome translocation demonstrated in relatively high frequency in other MALT lymphomas, particularly those of the lung, stomach, conjunctiva and orbit. However, other clonal cytogenetic abnormalities were demonstrated in the IPSID lymphoid cells of mesenteric lymph nodes, even in patients with early stage disease limited to the mucosa. In one patient, rearrangement resulted from translocation (9;14) in 21 out of 23 mitoses. The rearranged α1 gene fragment in that case was cloned and it was shown to contain...
Further molecular studies identified this chromosomal translocation as involving the Pax5 gene, which was later demonstrated to be associated with some cases of lymphoplasmacytic lymphoma, too.48 Another chromosomal abnormality demonstrated in a single IPSID case was t(2;14) involving band p12 on chromosome 2 in the vicinity of the κ chain gene locus. Other clonal abnormalities demonstrated in αHCD were a case of t(5;9) and another case of 14q+ chromosome.50 In a patient with leukemic manifestation of αHCD peripheral blood cytogenetics demonstrated an abnormal karyotype showing multiple reciprocal translocations including t(21;22) (q22;q11), which seems to be translocating the AML1 gene to the λ light chain locus.25 It is interesting also to note that the AML1 gene may be involved in some cases of multiple myeloma.51

Taken together, the relatively few cytogenetic studies in IPSID demonstrate clonal abnormalities involving the p32 heavy chain locus on chromosome 14 as well as the light chain loci on chromosomes 2 and 22, sharing features with both malignant lymphoma and immunoproliferative diseases.

Pathogenesis

The search for pathogenic factors was related to the well-known unique features of IPSID i.e. its ethnic and geographic distribution as well its response to antibiotics, at least in the early stages. A striking association of IPSID with human leukocyte antigens (HLA), AW19, A9 and B12 and the B blood group has been described.52,53 Genetic predisposition is further substantiated by the development of IPSID in relatives living apart53 and the presence of elevated intestinal isoenzyme alkaline phosphatase, a feature
of IPSID in healthy family members of some patients with IPSID. Occult defects of the cellular and humeral immunities have been detected in first degree, but otherwise healthy relatives of some patients with IPSID. It is difficult to decide whether these observations indicate a genetic predisposition or are due to shared environmental factors.

Recently, Lecuit et al demonstrated the presence of Campylobacter jejuni in the intestinal tissue obtained from a patient with IPSID who had a dramatic response to antibiotics. A follow up retrospective analysis of archival intestinal biopsy specimen disclosed Campylobacter species in four out of six additional patients with IPSID, using fluorescent in situ hybridization (FISH) and immunohistochemical techniques. However, this association has been challenged. C. jejuni is an initiating factor in chronic autoimmune disease such as Guillan-Barre Syndrome and reactive arthritis. It is not known to be a persistent colonizer of human gut, except in immunodeficient individuals. Besides, the temporal relation between C. jejuni and IPSID is unknown.

We believe that the association with C. jejuni can fit into a plausible working hypothesis for the pathogenesis of IPSID. Patients with IPSID seem to have an acquired immune deficiency state in the humoral and cellular immunity. They usually have serum immunoglobulin levels lower than matched controls, more than what is expected from protein losing enteropathy. They have impaired cellular immunity as demonstrated by low response to recall and sensitizing antigen, tuberculin, mumps and dinitrochlorobenzene (DNCB). The proportion of T-lymphocytes in IPSID patients is lower than normal, too. An in vitro study of the immunologic function of circulating mononuclear cells in six patients with IPSID who were in prolonged remission demonstrated varying degrees of defects in functions of B-lymphocytes, T-suppressor
cells, T-helper cells and natural killer cells; two of these cases have been treated with
tetracycline only. We have previously hypothesized that these immunologic immune
defects may be attributed to the modulatory effects of *V. cholerae* toxins acquired during
the epidemic that swept the same IPSID geographic areas during the early sixties. It is
interesting to note that the reports on IPSID started to appear in these areas a few years
after the Eltor cholera epidemic.

One can speculate too, that in the presence of continuous antigenic stimulation
within the gut and due to a presumed *C. jejuni* infection, IgA producing plasma cells
proliferate in the lamina propria of the small intestine. (Fig 1) Deletions and insertions
develop at a high rate (approximately 6%) of somatic mutation introduced into rearranged
*V_H* region genes during normal development of germinal center B-cells. Besides *C.
jejuni* cytolethal distending toxin is known to induce double- stranded-DNA breaks.
Under these circumstances occasional mutated B-cells may develop and differentiate into
aberrant plasma cells producing truncated αHC proteins. The absence of any variable
region determinants on the surface of these mutated B-cells may provide a selective
advantage by eliminating idiotype and allowing the cells to escape the normal immune
regulatory control. Continuing proliferation of these aberrant cells within the mucosa
gives the clinicopathologic picture of αHCD. Although the initiating events are still not
very clear, ongoing mutational events presumably involving Pax5 and/or other oncogenes
may lead to a neoplastic progression into lymphoplasmacytic and immunoblastic
lymphoma and to the full-blown lymphomatous phase of IPSID. (Fig 1)

**Treatment and Outcome (Table 3)**
Although spontaneous remissions occur in early stages, once established the untreated disease progresses relentlessly causing severe malabsorption and malnutrition. Early treatment is recommended to control the symptoms and hopefully slow, or prevent progression of the disease.60 The Tunisian/French group published a small prospective study of twenty-one Tunisian patients with IPSID all of whom underwent laparotomy and elaborate staging and investigative procedures.28 Six had early disease confined to the small bowel wall, thirteen had advanced disease with tumor formation and two were described as “intermediate”. The six patients with early stage disease responded well to antibiotics (tetracycline or metronidazole and ampicillin/tetracycline), while the remaining fifteen patients received anthracycline-based combination chemotherapy. The overall remission rate was 90 ± 12% at two years and 67 ± 25% at three years. All patients alive beyond 3.5 years were disease free. Another more recent small series from Turkey61 reported that tetracycline (1 gram daily) alone in seven early stage patients yielded 71% complete remission rate and 43% five year disease free survival rate (DFS). The other sixteen patients with intermediate or advanced disease received COPP chemotherapy (cyclophosphamide vincristine procarbazine and prednisone) followed by tetracycline 1 gram/per day for six months. Eleven of these sixteen patients achieved CR. The five year overall survival for the entire group was 70% and the five-year disease free survival for patients in CR was 75%. A treatment regimen was recommended by Rambaud and Halphen based on the review of about one hundred well documented cases from the literature including eighteen of their own. They recommended first line antibiotics, including tetracycline and metronidazole for early stage patients. Patients without marked improvement after a six month course of antibiotic or complete remission
within twelve months should be given CHOP (cyclophosphamide vincristine adriamycin and prednisone) chemotherapy. Chemotherapy was also recommended upfront together with antibiotics for patients with advanced disease at presentation. The average overall CR rate using this regimen was around 50% and the median survival was 67% at three years. This regimen also agrees with the clinical trials where anthracycline containing regimen was found to be superior to non-anthracycline regimen. Relapses of the low grade IPSID component may happen as expected and may be controlled by antibiotics alone. Whether maintenance antibiotic is necessary for a long period of time is not established. Life long suppression of antigenic stimulus has been proposed. Response to antibiotic diminishes with increasing dysplasia of the lymphoplasmacytic cells and with tumorous infiltration of the bowel wall and the mesenteric lymph nodes. In addition to marked clinical improvement and histological tumor regression by serial jejunal biopsies, response can be roughly quantitated by estimating the serum level of αHC protein. However, in some patients, large cell transformation or relapse may be associated with a stable or even declining αHC protein levels.

Surgery is usually reserved for a palliation of obstructing tumor masses or as a diagnostic and staging procedure. Total abdominal radiation has been recommended in bulky abdominal disease with some reported remissions. Unresponsive disease progresses relentlessly at a variable pace and most patients die of malnutrition, sepsis, intestinal obstruction and other disabling complications secondary to massive involvement of the bowel and abdominal cavity by tumor. Intensive chemotherapy and autologous bone marrow transplant was recommended for patients with advanced or
refractory disease but to our knowledge there are no reports in the literature demonstrating the utility of bone marrow or hematopoietic cell transplant in IPSID.

**Future Investigations:**

We believe that the more recent discoveries in the molecular pathogenesis of IPSID raise some important questions that can be answered only by cooperative international studies. The real incidence and the geographic distribution of IPSID needs to be better defined. Studies from the Middle East indicate a decline in the incidence of IPSID over the last three decades, a phenomenon which could not be totally explained by improved socioeconomic and hygienic conditions. International cancer registry comparative studies are needed to document this decline, and an attempt be made to explain it. The role of *C. jejuni* and maybe other bacterial organisms including *V. cholerae* needs more clinicopathologic and experimental studies. The contribution of double-strand-DNA breaks caused by *C. jejuni* toxin to carcinogenesis is an important topic for future studies, since that organism is relatively prevalent all over the world.

The frequent occurrence of deletions and duplications during somatic hypermutations occurring normally in the germinal center B-cells has been implicated for oncogene translocations in Burkitt lymphoma as well as αHCD. Abdominal and intestinal Burkitt lymphomas are relatively common childhood tumors in the same geographic areas as IPSID. Malaria was eradicated in these areas for many years thus the high frequency of Burkitt lymphoma cannot be blamed on endemic malaria as in Africa. More than two decades ago, we envisioned a common pathway for the pathogenesis of these two types of lymphoma with Burkitt lymphoma developing due to an EBV infection in children previously not exposed to EBV and IPSID developing due to...
another presumed infection in young adults immune to EBV. (Fig 1) We speculate that chronic *C. jejuni* infection can explain the high incidence of IPSID in young adults versus Burkitt lymphoma, which is EBV related in children. However, more studies are needed to clarify the mechanism(s) involved in IPSID and intestinal Burkitt lymphoma whether they are immunomodulatory and/or initiating events.

The role of Pax5 in the pathogenesis and progression of IPSID lymphoma is worth investigating, too. Pax5 gene encoding the transcription factor BSAP is required for progression of B-lymphopoiesis beyond the pro-B stage. Plasma cell differentiation involves repression of Pax5. Pax5 translocations and mutations are involved to a certain degree in the closely related lymphoplasmacytic lymphoma, as well as in multiple myeloma. Another interesting molecular feature of IPSID is the observation that the αHCD protein is restricted to α1 species. This can be attributed to the *C. jejuni* antigenic drive. Another possibility could be related to the fact the α2 chains are quickly degraded resulting in the “non-secretory” form αHCD.

New clinical trials are needed in light of the recent discoveries regarding *C. jejuni* association with IPSID. Previous trials have not incorporated anti CD20 (rituximab) in the management of IPSID. As expected, the centrocyte-like cells are CD20 positive, but the plasma cells are not. The role of rituximab in IPSID is worth investigating both in the early and the advanced large cell IPSID. Besides, it would be interesting in light of the extreme plasma cell differentiation and the plasmacytic nature of the large cell IPSID lymphoma to investigate a possible role for newer multiple myeloma therapies including proteasome inhibitors at least in refractory cases.
We believe that further investigations of IPSID can yield additional information contributing to the understanding of the molecular biology as well as clinical aspects and managements of the mature B-cell neoplasms in general.
References:


64. Al-Saleem T. Pathology and time trend of the Mediterranean type of MALT lymphoma., 87th Annual Meeting American Association of Cancer Research, 1996.


66. Almasri NM, al-Abbadi M, Rewaily E, Abulkhair A, Tarawneh MS. Primary gastrointestinal lymphomas in Jordan are similar to those in Western countries. Mod Pathol 1997; 10:137-41.


Table 1. Subtypes of 202 primary non-Hodgkin lymphomas of the small intestine in Iraq pathologically diagnosed by the senior author during a 13-year period (1973-1985) – association with α heavy chains

<table>
<thead>
<tr>
<th>LYMPHOMA TYPE</th>
<th>NO. (%)</th>
<th>α HEAVY CHAINS+/TESTED (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSID (EARLY)</td>
<td>25 (12%)</td>
<td>13/19 (68%)</td>
</tr>
<tr>
<td>IPSID (ADVANCED)**</td>
<td>77 (38%)</td>
<td>17/52 (33%)</td>
</tr>
<tr>
<td>TOTAL: IPSID</td>
<td>102 (50%)</td>
<td>30/71 (42%)</td>
</tr>
<tr>
<td>NON IPSID LYMPHOMA</td>
<td>25 (12%)</td>
<td>0/17 (0%)</td>
</tr>
<tr>
<td>BURKITT LYMPHOMA</td>
<td>73 (36%)</td>
<td>0/28 (0%)</td>
</tr>
<tr>
<td>INTESTINAL T-CELL</td>
<td>2 (1%)</td>
<td>0/1 (0%)</td>
</tr>
</tbody>
</table>

* Tested in the serum by immunoselection
**IPSID associated large cell lymphoma
Table 2. Clinical, laboratory and radiological findings in IPSID 2-4, 14, 18, 20, 22, 76, 77

<table>
<thead>
<tr>
<th>Symptoms &amp; Signs:</th>
<th>% of Patient’s affected:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>80-100%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70-100%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>90-100%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10% (early stage); 30% (advanced stage)</td>
</tr>
<tr>
<td>Low grade fever</td>
<td>30-50%</td>
</tr>
<tr>
<td>Abdominal masses</td>
<td>20% (early stage); 60% (advanced stage)</td>
</tr>
<tr>
<td>Clubbing of fingers</td>
<td>20-60%</td>
</tr>
<tr>
<td>Hepatomegaly, splenomegaly or peripheral lymphadenopathy</td>
<td>Rare (3-5%) except in very advanced disease</td>
</tr>
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Laboratory findings:

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<table>
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<tbody>
<tr>
<td>Alpha heavy chain protein (see text)</td>
<td>40-100%</td>
</tr>
<tr>
<td>Low serum immunoglobulins &amp; albumin</td>
<td>common*</td>
</tr>
<tr>
<td>High alkaline phosphatase (intestinal isoenzyme)</td>
<td>common*</td>
</tr>
<tr>
<td>Sugar &amp; fat malabsorption</td>
<td>60-80%</td>
</tr>
<tr>
<td>Hypocalcemia &amp; hypomagnesemia</td>
<td>common*</td>
</tr>
<tr>
<td>Anemia (mild to moderate)</td>
<td>30-50%</td>
</tr>
<tr>
<td>Parasitic infestations, especially Giardiasis</td>
<td>very common*</td>
</tr>
</tbody>
</table>

Radiological Findings (Barium)

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<table>
<thead>
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<tbody>
<tr>
<td>Malabsorption pattern, edema and “postage stamp appearance” of duodenal folds</td>
<td>common early stage*</td>
</tr>
<tr>
<td>Multiple filling defects, ulceration, strictures and enlarged mesenteric lymph nodes by CT scan</td>
<td>common advanced stage*</td>
</tr>
</tbody>
</table>

* exact numbers are not available
### Table 3. Treatment Options and Response of IPSID

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>Treatment</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Early bowel wall involvement, No visible tumor</td>
<td>1. Antibiotics: tetracycline, 1gm/day for 6 months&lt;sup&gt;16, 17, 19, 22&lt;/sup&gt;</td>
<td>30-70% CR lasting months to several years</td>
</tr>
<tr>
<td></td>
<td>2. Metronidazole plus ampicillin/tetracycline&lt;sup&gt;61&lt;/sup&gt;</td>
<td>43% five year DFS</td>
</tr>
<tr>
<td></td>
<td>3. H. pylori regimen for 7 days (1 patient)&lt;sup&gt;78&lt;/sup&gt;</td>
<td>5+ months</td>
</tr>
<tr>
<td></td>
<td>4. C. Jejuni treatment with H. pylori regimen for 5 months (1 patient)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>12+ months</td>
</tr>
<tr>
<td>2. Advanced disease with bowel wall tumor formation ± mesenteric node involvement</td>
<td>Anthracycline-based combination chemotherapy ± tetracycline&lt;sup&gt;38, 62, 64&lt;/sup&gt;</td>
<td>50-60% C lasting months to years (60-70% DFS at 3 years)</td>
</tr>
<tr>
<td>3. Advanced bulky tumor with mechanical complications</td>
<td>Corrective surgery, palliative radiation therapy, combination chemotherapy&lt;sup&gt;16, 19, 22&lt;/sup&gt;</td>
<td>Partial response, few months to less than 1 year</td>
</tr>
</tbody>
</table>
Legend

Figure 1
A hypothetical scheme for the pathogenesis and progression of immunoproliferative small intestinal disease and intestinal Burkitt lymphoma. Chronic *C. jejuni* infection develops due to defective gut mucosal immunity. The cytolethal distending toxin of *C. jejuni* may cause double stranded DNA breaks in proliferating germinal center B-cells which are even normally liable for mutations, deletions and insertions. Truncated α heavy chain producing plasma cells are selected due to the absence of variable determinants on the surface, they proliferate and progress resulting in IPSID. EBV infection in previously unexposed children may result in Burkitt lymphoma of the intestine.

**A:** immunoselection, abnormal precipitation lines in patient’s sera (1 & 2), and normal control showing precipitation around the trough (3).

**B:** (electron micrograph) IPSID neoplastic plasma cells with distended endoplasmic reticulum and intranuclear “inclusions” (Dutcher bodies).

**C&D:** jejunal biopsies of early IPSID showing diffuse mucosal plasma cell proliferation with intact epithelium with sparse crypts (H&E stain).

**E:** progressed IPSID mesenteric lymph node: lymphoplasmacytic and immunoblastic lymphoma (Giemsa stain).

**F:** autopsy thickened intestinal wall along the whole length and enlarged mesenteric lymph nodes.

Figure 2
Alpha heavy chain protein molecular structure of IPSID (B) compared to normal IgA molecule (A). The dotted areas represent deleted variable and first constant regions of amino terminus of the heavy chain (blue) as well as missing entire light chain (orange). The normal structure of the immunoglobulin molecule resumes at the beginning of the hinge region (green). The carboxy terminal (COO-) portion of the polypeptide is intact. Joining chains, present in a majority of the IPSID alpha heavy chain proteins are not shown in the diagram.16
childhood infections + V. cholerae toxin?
Defective gut mucosal immunity?

C. jejuni infection

cytotoxic distending toxin

double-stranded DNA breaks?
c-myc translocation
Burkitt Lymphoma?
EBV

polyclonal plasma cells
mutations, deletions, insertions

Truncated alpha heavy chain producing plasma cells

selection due to escape from normal immune regulation control?

Massive proliferation of αHC-producing plasma cells limited to the mucosa (IPSID)

progression
multicentric lymphoplasmacytic and immunoblastic lymphomas
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Immunoproliferative small intestinal disease (IPSID); a model for mature B-cell neoplasms

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