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Follicular Centre Cell Lymphoma with Alpha Heavy Chain Disease

A Histopathological and Immunohistological Study

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Summary. The first recorded case of a small intestinal lymphoma with alpha heavy chain disease occurring in Hungary is reported. The clinical manifestation of the disease and the focal distribution of mucosal alterations do not fulfill the criteria to make a diagnosis of Mediterranean type lymphoma (MTL) but the lymphomatous segments of the jejunum show the same pathological and immunohistological characteristics as seen in MTL. One of the basic features of MTL, the so called lympho-histiocytic nodules, which have been suspected by previous authors to represent an incipient neoplastic process involving histiocytic cells, is identified as follicular centroblastic/centrocytic malignant lymphoma. The cytogenetical connection between the massive proliferation of abnormal alpha chain producing plasma cells and neoplastic germinal centres is substantiated by direct immunohistological evidence using a combined immunofluorescent and immunoperoxidase technique to detect heavy and light chains within the same cell. The sarcomatous-appearing pleomorphic cell proliferation is interpreted as an anaplastic change in the centroblastic/centrocytic lymphoma. Unequivocal evidence for an abnormal IgA production in this pleomorphic component has not been obtained. Our observations suggest that in alpha heavy chain disease the neoplastic cell population originates in the germinal centres.

Key words: Mediterranean type lymphoma – Alpha chain disease – Histopathology – Immunohistology

Introduction

In 1964 Franklin et al. recorded a patient with malignant lymphoma whose serum contained a peculiar protein that reacted as a gamma globulin, but which on immunoelectrophoresis failed to show evidence of light chains. Soon after the initial report four cases of gamma heavy chain disease were recorded by Osserman and Takatsuki (1964).

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In 1968 Rambaud et al. und Seligmann et al. (1968) gave the first account of alpha heavy chain disease. The alpha chain disease is commonly associated with the clinicopathological entity known as Mediterranean type lymphoma (MTL) (Ramot et al. 1965; Eidelmann et al. 1966). This suggests that the two diseases are identical and that alpha chains have merely not been looked for in most cases of MTL (Seligmann 1975).

The relation between the malignant cell population and the massive infiltrate of plasma cells carrying the IgA abnormality in MTL is not known (Rappaport et al. 1972). A detailed histopathological and immunohistological study of an intestinal lymphoma with alpha heavy chain disease, reported herein, offers new insights into the pathogenesis of the disease.

Case Report

S.B., a 48-year-old man, presented with a history of gastric ulcer and a weight loss of more than 20 kg within a few months in October 1977. Signs of clinical malabsorption, e.g. diarrhoea and steatorrhoea, were lacking, therefore standard tests for malabsorption have not been performed. Roentgenographic examinations obtained on admission confirmed the presence of gastric ulcer. At laparotomy, a small healing ulcer was noted in the prepyloric region and there were extensive nodular lesions in a 30 cm segment of the proximal jejunum, 25 cm from the Treitz ligament. The mesenteric nodes were enlarged. There was no hepatosplenomegaly. Resection of the tumorous jejunal segment with restorative anastomosis was carried out. One of the enlarged mesenteric lymph nodes and the normal-appearing appendix were also removed. The histologic diagnosis was intestinal lymphoma without mesenteric node involvement. Bone marrow biopsy and lymphangiography were normal. Using the Ann Arbor classification for staging, the case was stage I_E (confined to the viscus). Routine immunoelectrophoresis using polyvalent antiserum to human normal serum did not reveal any abnormal serum protein. He was given combined chemotherapy according to the VEP protocol. The check-up peroral duodenum biopsy in May 1980 did not show histological signs of relapse. He is still living over 3 years postoperatively.

Materials and Methods

Surgical material obtained from jejunum, mesenteric lymph node and appendix were cut into pieces immediately after removal to ensure adequate fixation. Routine formalin fixation (unbuffered) and paraffin embedding were carried out. Paraffin sections were stained with periodic acid-Schiff, reticulin and Giemsa stains in addition to haematoxylin and eosin. Immunohistology was performed both on trypsinized (Mepham et al. 1979) and on undigested sections. Immunoglobulins were demonstrated by indirect immunofluorescence (IF) and peroxidase – anti-peroxidase (PAP) techniques (Curran and Gregory 1978). Anti human alpha, delta, gamma and mu heavy chain-, as well as kappa and lambda light chain-antisera were used (DAKO immunoglobulins, Ltd., Copenhagen, Denmark). For a simultaneous detection of light and heavy chains a combined IF-PAP method was employed (Lechago et al. 1979). Immunofluorescence was examined in incident light by a Leitz Orthoplan microscope equipped with Ploemopak epiilluminator. The PAP reaction was observed in transmitted light either simultaneously or alternatingly.

Pathologic Observations

Gross Findings. The surgically removed jejunal segment was 28 cm long. The mucosa was focally thickened and irregular. No ulceration was found. Multiple grey-white tumorous nodules involved all the wall to the serosal surface and caused narrowings of the lumen. The mesenteric node was the size of a large

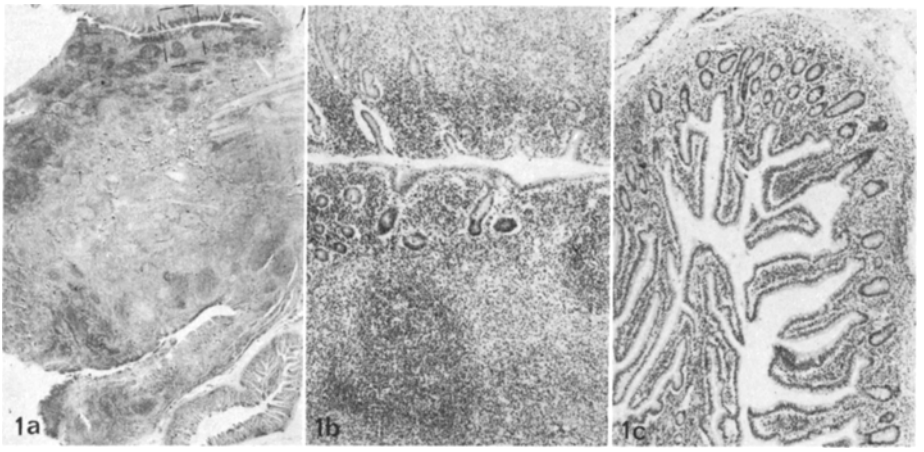


Fig. 1. a Jejunum showing tumor involvement and adjacent mucosa (bottom, right) Haematoxylin-eosin (×6.3). **b** Superficial area of the mucosa in the tumorous region indicated on a. The massive plasmacytic infiltrate of the lamina propria is band-like, due to the obliteration of the villous architecture. Haematoxylin-eosin (×50). **c** The villous pattern of the non-neoplastic segment (*bottom, right* on a) is preserved. Haematoxylin-eosin (×50)

bean and of moderately firm consistency. The appendix was 6 cm long, with no remarkable features.

Microscopic Findings. The non-lymphomatous intestinal mucosa showed intact villi and mucosal folds (Fig. 1a and 1c). The tumorous nodules were covered with a flattened mucosa. The lamina propria was heavily infiltrated by mature-looking plasma cells without significant imparement of the surface epithelium (Fig. 1a and 1b). In addition to the band like infiltrate in the lamina propria, mature-looking plasma cells formed broad trabeculae in the submucosa and in the muscularis propria.

Subjacent to the band like infiltrate of plasma cells in the lamina propria, the lymphomatous involvement took the form of fairly discrete nodules that often encroached on the submucosa. At low magnification, the nodules bore some resemblance to reactive lymphoid follicles (Fig. 2a) but could be distinguished by their rather ill-defined borders and their neoplastic germinal centres. These germinal centres did not exhibit zonal architecture, lacked starry sky cells and contained predominantly medium-sized neoplastic centrocytes characterized by wrinkling or indentation of their nuclear membrane, fine chromatin, small nucleoli and no visible cytoplasm (Fig. 2b). They were surrounded by an ill-defined rim of small lymphocytes. Some of these neoplastic germinal centres showed a focal or extensive plasmacytic transformation (Fig. 3). In the deeper layer of the submucosa the follicles did not contain plasma cells. They were larger than those in the superficial regions and lay "naked" in a pleomorphic lymphoid proliferation.

The interfollicular tissue was composed of monomorphic sheets of mature-looking plasma cells which occasionally showed large PAS – positive intracyto-

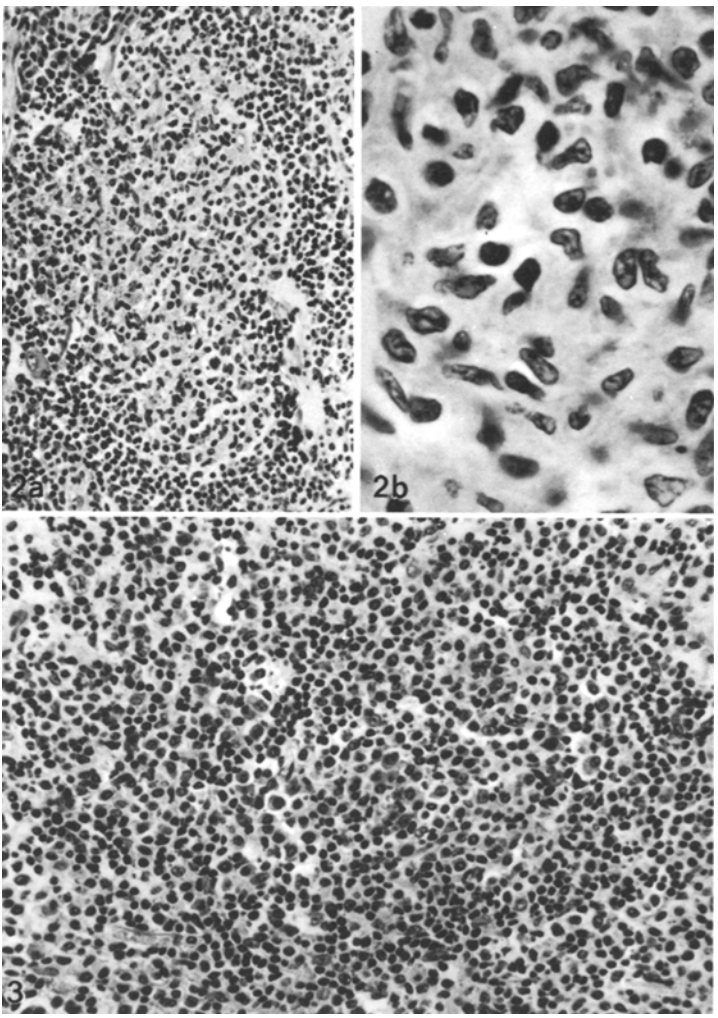


Fig. 2. **a** Neoplastic follicle from the lymphomatous growth with centrocytic germinal centre and ill-defined rim of small lymphocytes. Haematoxylin-eosin (×160). **b** Neoplastic centrocytes with marked nuclear irregularities. Haematoxylin-eosin (×800)

Fig. 3. Extensive plasmacytic transformation in a neoplastic germinal centre. Haematoxylin-eosin (×320)

plasmic inclusions, and of a sarcomatous-appearing pleomorphic lymphoid proliferation (Fig. 4a). This pleomorphic proliferation was made up of numerous large atypical immunoblast-like cells with vesicular nuclei, prominent eosinophilic nucleoli and abundant cytoplasm. The nuclei of these large blast cells were occasionally lobated and very similar to Sternberg-Reed giant cells (Fig. 4b). The proliferation as a whole did not suggest Hodgkin's disease. Most of the cells showed plasmacytoid features, i.e. abundance of cytoplasm and excentric

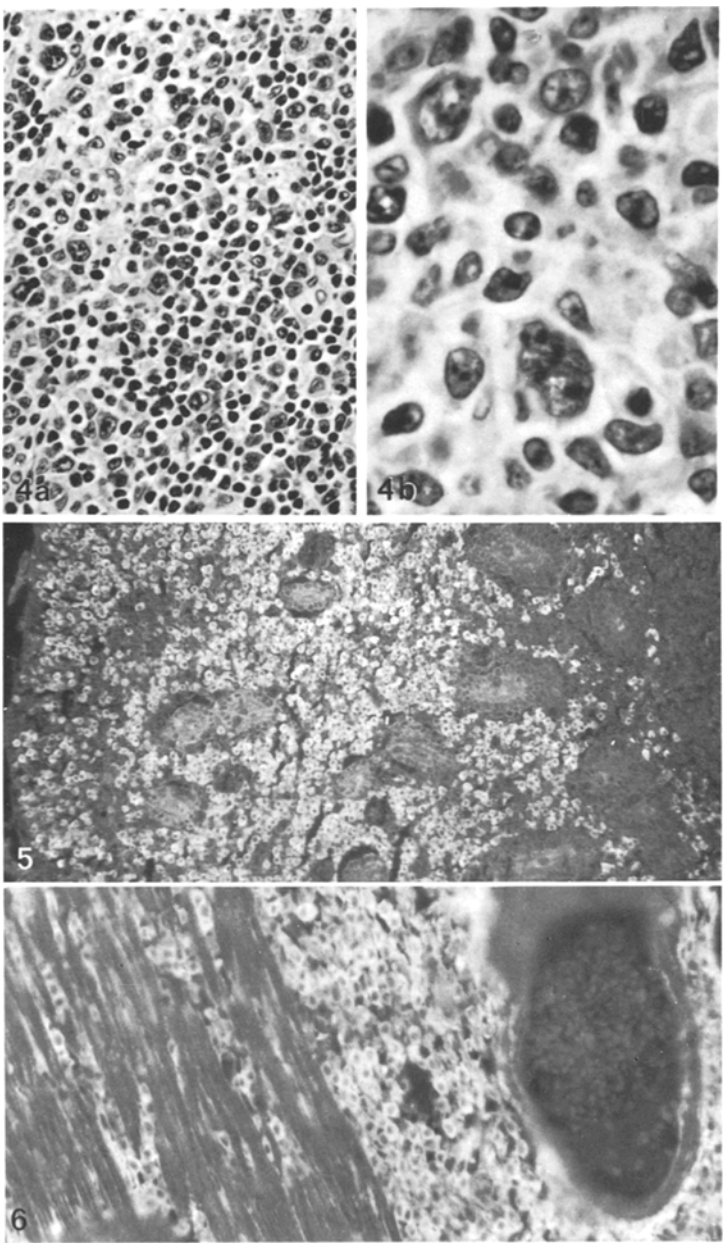


Fig. 4. a Diffuse pleomorphic proliferation containing atypical immunoblast-like cells and a Sternberg-Reed type giant cell (*top, left*) in addition to centroblasts and centrocytes. Haematoxylin-eosin ×320. **b** Immunoblast-like cells with plasmacytoid features and a Sternberg-Reed type giant cell. Haematoxylin-eosin (×1,000)

Fig. 5. Dense accumulation of alpha chain positive plasma cells in the upper part of the mucosa (*left*). The mid-zone of the gut (*right*) is mostly non-reactive. *IF* (×130)

Fig. 6. Dense infiltrate of alpha chain positive plasma cells in the muscularis propria. *IF* (×260)

location of nuclei. The pleomorphic infiltrate also contained numerous centroblasts and centrocytes, as well as mature and immature plasma cells. Mitoses were frequent.

Eosinophils were numerous in the mucosa of lymphomatous lesions. In one of the neoplastic growths, immediately below the level of the crypts of Lieberkühn, there were focal collections of eosinophils surrounded by histiocytes with granuloma – like appearance.

The appendix showed normal histology. The lumen contained fecal material and mature forms of *Enterobius vermicularis*.

The structure of the mesenteric lymph node was preserved (Fig. 12). There were numerous reactive follicles in the subcapsular cortex with moderately developed germinal centres. The paracortex contained small lymphocytes and scattered histiocytes with clear cytoplasm. The medullary sinuses were filled with sinus-histiocytes. Collections of mature plasma cells were seen in the cortex and in medullary cords.

The duodenal mucosa of the check-up peroral biopsy in 1980 was of medium thickness and with regular villous pattern. The lamina propria was loosely infiltrated by numerous plasma cells, neutrophils and eosinophils. There were some primary lymphoid follicles in the deepest layer of the lamina propria.

Immunohistological Observations

The most extensive immunohistological reactivity was obtained with alpha heavy chain specific antiserum. At low magnification, a massive band-like reaction was seen in the lamina propria (Fig. 5). The mid-zone of the jejunal wall containing the neoplastic follicles was non-reactive except for focal accumulations or scattered positive cells in the interfollicular tissue. There was a massive but discontinuous reactivity also in the muscularis propria (Fig. 6). At higher magnification, the massive reactivity was located in a monotonous population of plasma cells. The cytoplasm exhibited a moderate, the Golgi region a strong immunofluorescence (Fig. 10a). The PAP reaction product was weak in the cytoplasm and moderate in the Golgi region. Controlled trypsinization (optimum: 15 min) improved the PAP reaction somewhat but had no effect on immunofluorescence. The immunohistological reaction in these plasma cells did not reach the usual intensity of reactive plasma cells. In the mid-zone, neoplastic germinal centres with plasmacytic transformation also gave a positive reaction (Fig. 7). Some of the neoplastic follicles were surrounded by a similarly reacting rim of plasma cells. Occasional neoplastic germinal centres showed a weak intracytoplasmic positivity in a few centrum cells (Fig. 8). Immunoblast-like cells of the interfollicular tissue did not react with alpha heavy chain specific antiserum, but plasma cells scattered among them were often positive. Sternberg-Reed like giant cells were invariably negative with the PAP technique. The immunofluorescent technique, however, showed an occasional intracytoplasmic positivity in these giant cells (Fig. 11).

Mixed light chain specific (kappa + lambda) antiserum revealed only scattered plasma cells in the lamina propria and the muscularis propria was devoid of light chain positive cells. Thus the bulk of alpha heavy chain positive cells

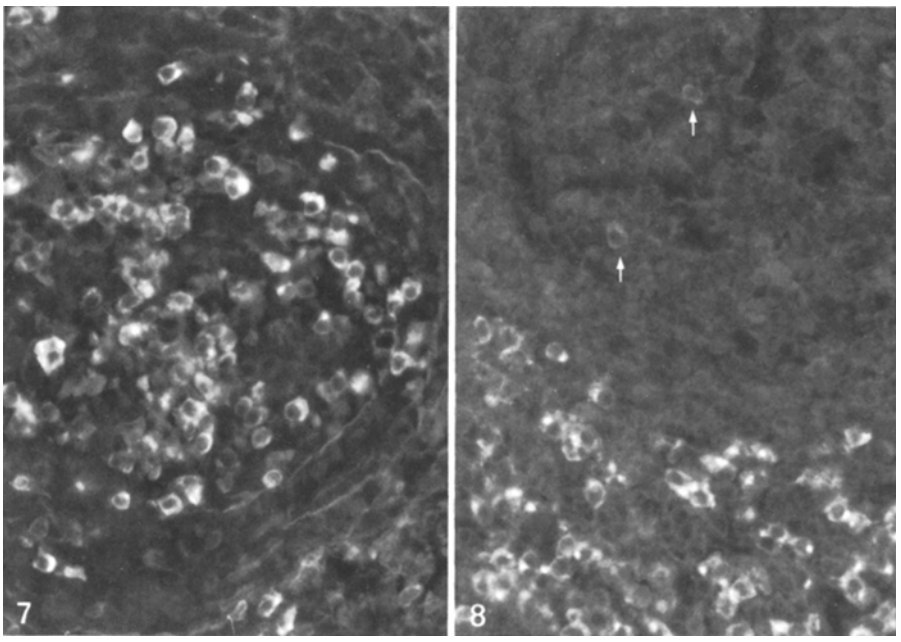


Fig. 7. Neoplastic germinal centre showing extensive plasmacytic transformation. Alpha chain demonstration by *IF* (× 320)

Fig. 8. Neoplastic germinal centre without plasmacytic transformation. Some weakly alpha chain positive centrum cells in the germinal centre (*arrows*). Accumulation of alpha chain positive plasma cells in the interfollicular tissue (*bottom*). *IF* (× 320)

did not contain light chains. Light chain reactive cells were more numerous in the interfollicular tissue of the mid-zone, but only plasma cells could be identified; immunoblast-like cells and Sternberg-Reed like giant cells were not seen.

There was no immunohistological reactivity with delta and mu heavy chain specific antisera. The gamma heavy chain specific antiserum, however, demonstrated strongly positive plasma cells in those regions where light chain positive plasma cells were found. Immunoblast-like cells and Sternberg-Reed like giant cells were negative. The combined IF-PAP technique for the simultaneous demonstration of gamma heavy chains and light chains gave direct evidence that gamma heavy chains and light chains were present in identical plasma cells (Fig. 9a and b). This finding proved in addition, that IF and PAP reactivity did not quench one another when present in the same cell.

Combining IF for alpha heavy chain demonstration and PAP for mixed light chains, it could be established that normal IgA-producing plasma cells were lacking in regions with lymphomatous involvement (Fig. 10a and b). The adjacent normal-appearing intestinal mucosa, in turn, contained a number of normal alpha chain positive/light chain positive plasma cells mixed with the abnormal alpha chain positive/light chain negative population. The combined

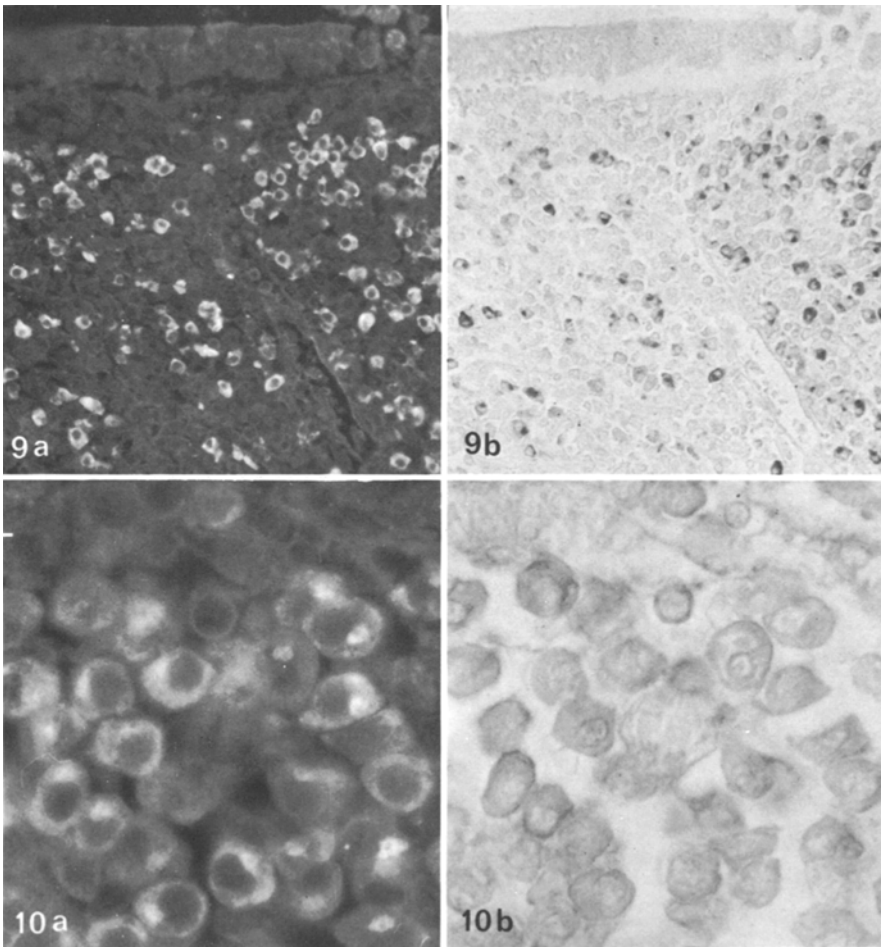


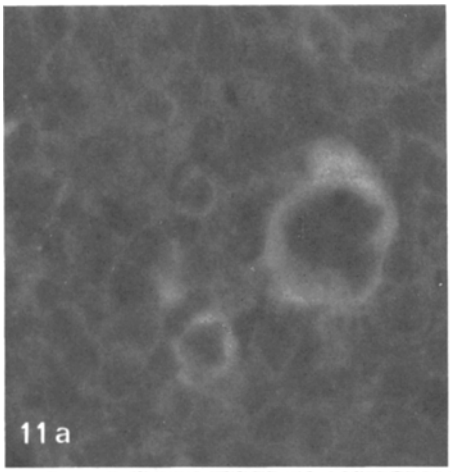
Fig. 9. a Scattered gamma chain positive plasma cells in the upper part of the mucosa. *IF* (×200). **b** The same cells show light chain positivity with mixed light chain antiserum. PAP (×200)

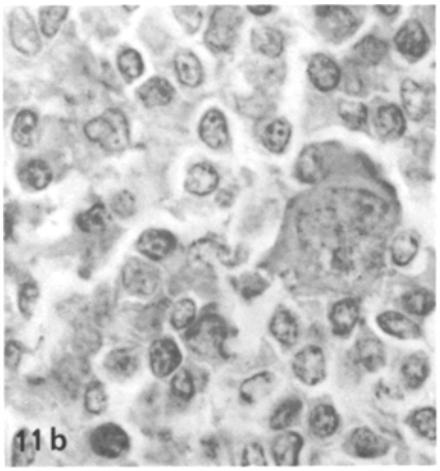
Fig. 10. a Dense accumulation of alpha chain positive plasma cells showing moderate cytoplasmic and intense Golgi-zone fluorescence. *IF* (×800). **b** These abnormal alpha chain positive cells are negative with mixed light chain antiserum. PAP (×800)

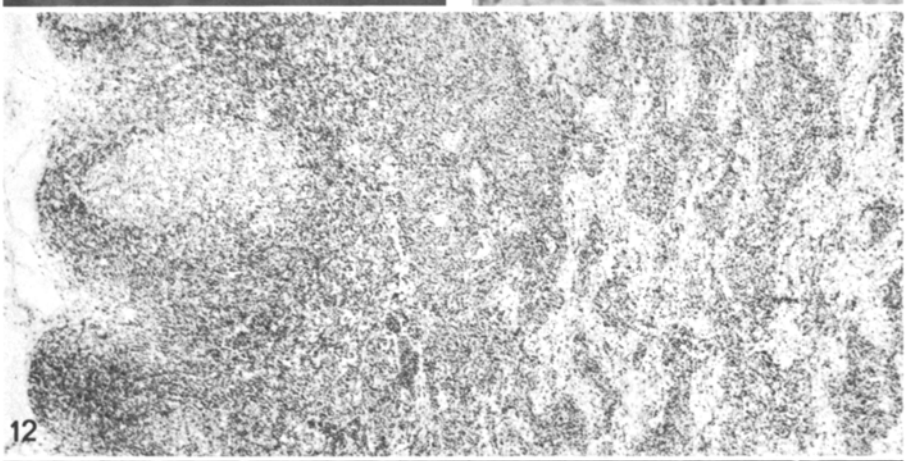
IF-PAP technique failed to reveal light chains in occasional alpha heavy chain positive Sternberg-Reed like giant cells (Fig. 11a and b).

Examination of the check-up peroral duodenum biopsy with the alpha heavy chain – mixed light chain combination revealed that the alpha chain positive plasma cells of the lamina propria invariably contained light chains.

The mesenteric lymph node showed mostly gamma heavy chain positive/light chain positive plasma cells (Fig. 13). Alpha heavy chain positive plasma cells were lacking in the cortical region and very scarce in the medullary cords. The alpha chain positive plasma cells were devoid of light chains.







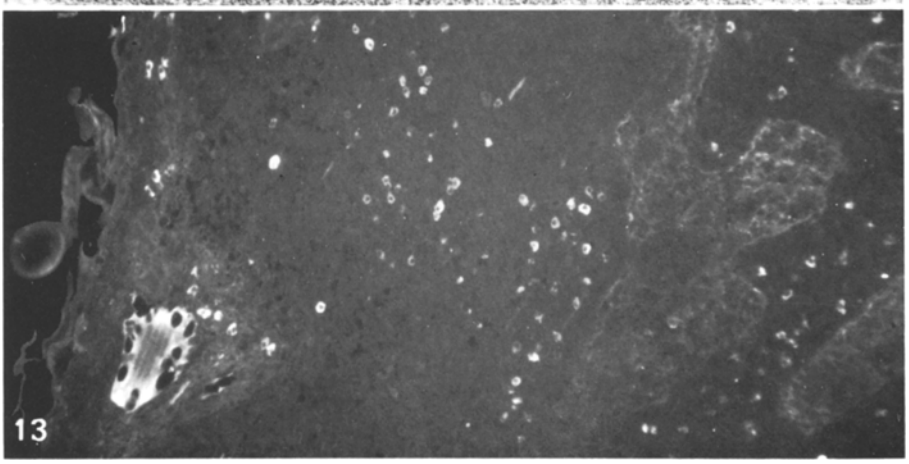


Fig. 11. a A weak diffuse intracytoplasmic positivity for alpha chain in a Sternberg-Reed type giant cell and in some plasmacytoid cells. *IF* (× 800). **b** No light chain positivity can be demonstrated in these cells with mixed light chain antiserum. PAP-haematoxylin (× 800)

Fig. 12. Mesenteric lymph node with reactive follicles in the subcapsular cortex (*left*). Diffuse lymphocytic fields in the paracortex (*middle*). Prominent medullary cords and dilated sinuses (*right*). Haematoxylin-eosin (× 50)

Fig. 13. Foci of gamma chain positive plasma cells in the paracortex. Scattered gamma chain positive plasma cells in the medullary cords. The histiocytes of medullary sinuses also show a weak to moderate intracytoplasmic reaction for gamma chain. *IF* (× 130)

Discussion

Gastrointestinal lymphoma is an extremely common disease in the Middle East where it is often associated with malabsorption and alpha heavy chain disease. The histopathology of these tumors is poorly characterized and their relationship to the newer lymphoma classifications and thus to gastrointestinal lymphoma as it occurs in "Western" countries is poorly understood (Isaacson 1981). Among the large numbers of gastrointestinal lymphomas occurring in the Middle East an as yet undefined proportion is characterized by malabsorption and a diffuse mature plasmacytic infiltrate in the lamina propria of the intestine. To this group the terms Mediterranean type lymphoma (MTL) or IPSID (immunoproliferative small intestinal disease) have been applied (World Health Organization 1976).

It appears that a band-like massive plasmacytic infiltrate (MPCI) in the lamina propria and Mediterranean type lymphoma are two distinct phases in the development of IPSID. In MTL jejunal and/or mesenteric lymphoma is observed in addition to MPCI (Rappaport et al. 1972; Lewin et al. 1976). Alpha heavy chain disease is commonly associated with MPCI or MTL. It is unknown, however, whether all cases of MPCI and MTL are to be interpreted as alpha heavy chain disease. Seligmann (1975) and others (Rambaud and Matuchansky 1973; Zlotnik and Levy 1974) believe that all patients with MTL have alpha heavy chain disease but that in some of these patients the pathological immunoglobulin may only be demonstrated in the plasma cells and not in the serum or jejunal fluid. Alpha chain disease in some instances may be of a non-secretory nature (Rambaud et al. 1980).

The reported case is the first alpha heavy chain disease recorded in Hungary. It is associated with an unusual manifestation of intestinal lymphoma. It does not fulfill criteria to make a diagnosis of MTL or IPSID (Isaacson 1981) since clinical malabsorption is lacking and the villous architecture of the non-lymphomatous jejunal mucosa is preserved. Although the clinical aspects of the disease (the patient is much older than the usual cases of "Mediterranean" type lymphoma and does not have an apparent malabsorption) suggest a "Western" type of primary intestinal lymphoma (Lewin et al. 1976) the qualitative pathological and immunological features are typical of a "Mediterranean" type of primary intestinal lymphoma. The disease involves the proximal jejunum in contrast to the midjejunal involvement in the "Western" type lymphoma (Rappaport et al. 1972). The massive plasmacytic infiltrate in the lamina propria with severe abnormalities of the villous architecture, characteristic of MTL, is present in the lymphomatous segments of the jejunum (but due to its focal distribution does not appreciably interfere with the absorptive function of the small intestine). The lymphomatous segments contain both an atypical nodular proliferation and a diffuse pleomorphic population with sarcomatous appearance as described in MTL (Rappaport et al. 1972; Lewin et al. 1976).

It is yet uncertain whether the mature plasma cell infiltrate in IPSID represents a neoplastic condition or not. The mechanism by which overt lymphoma evolves is unclear and there is some disagreement over the nature of this lymphoma.

Rappaport et al. (1972) classify the majority of malignant lymphomas in MTL as histiocytic type (11/16) and list Hodgkin's disease second in frequency (3/16). According to Lewin et al. (1976) and others (Eidelmann et al. 1966; Bonomo et al. 1972; Seligmann and Rambaud 1969; Shahid et al. 1975; Tabbane et al. 1976) malignant lymphomas in MTL correspond most closely to Rappaport's diffuse mixed variety and label them pleomorphic lymphomas. These differences in classification are probably related to the identification of the malignant cell population. Rappaport et al. (1972) consider only the large cell component as neoplastic. Lewin et al. (1976), in turn, regard the malignant cell population as essentially mixed, including small lymphocytic, larger histiocytic and Sternberg-Reed type cells and even plasmacytoid cells.

Previous reports are uncertain as to the significance of the so called lympho-histiocytic nodules. Rappaport et al. (1972) observed such nodules in 3 of their 4 premalignant MTL cases and in 3 of their 11 histiocytic type malignant MTL cases. Lewin et al. (1976) found them in all of their premalignant MTL cases, in 4 of their 14 malignant MTL cases an in 1 of their 3 alpha chain disease patients. Rappaport et al. (1972) raised the possibility that these nodules might represent an incipient neoplastic process involving the histiocytic cells. Lewin et al. (1976) concur in this opinion.

The *three basic histopathological features* of MTL are present in our case: massive infiltration by mature-looking plasma cells, atypical nodular proliferation and a diffuse pleomorphic cell population with sarcomatous appearance. These features cannot be interrelated within the framework of Rappaport's classification (Rappaport 1966). No cytogenetical connection can be established between plasma cells and "histiocytic" cells. On the basis of functional lympho-ma-classifications (Lukes and Collins 1974; Gérard-Marchant et al. 1974; Lennert and Mohri 1978) it is obvious, however, that the so called lympho-histiocytic nodules are in fact neoplastic follicles. The atypical nodular proliferation corresponds to a centroblastic/centrocytic lymphoma.

Many cases of centroblastic/centrocytic malignant lymphoma develop into "sarcomas". This fact has long been recognized and led to the unfortunate term "preblastomatosis" for follicular lymphomas. Actually, the process is malignant from the beginning (Lennert and Mohri 1978). It is merely that the degree of malignancy is low at first but later there is often transformation into highly malignant lymphoma. This transformation is coupled with a blastic change. In our case, the pleomorphic interfollicular proliferation containing atypical immunoblast-like cells and Sternberg-Reed like giant cells represents transformation into high grade malignancy. Plasmacytoid features in the diffuse pleomorphic cell population of MTL is quite common (Rappaport et al. 1972; Lewin et al. 1976). Lennert called this population immunoblastic lymphoma with plasmacytoid or plasmacytic differentiation (Lennert and Mohri 1978).

Lukes et al. (1978) state that they have seen immunoblastic sarcomas develop in patients with Sjogren's syndrome, Hashimoto's disease, alpha chain disease, gluten-sensitive malabsorption, in graft recipients, immunodeficiency states and senescence. It is often assumed that, regardless of morphology, lymphomas developing in such patients are by definition immunoblastic sarcomas (Nathwani et al. 1978). To label any large cell lymphoma with basophilic cytoplasm an

immunoblastic sarcoma will result in the inclusion of tumors of diverse origin. Isaacson et al. (1980) state that due to the abandonment of the strict morphological criteria for the diagnosis of this tumor (Lukes and Collins 1974) immunoblastic sarcomas seem to have achieved the same meaningless status as the term "reticulum cell sarcoma".

It would be unjustifiable to treat the diffuse sarcomatous-appearing cell proliferation isolated from other histopathological components of the disease and label it immunoblastic lymphoma with plasmacytic or plasmacytoid differentiation. In our case, the pleomorphic proliferation is to be interpreted as an anaplastic change evolving in centroblastic/centrocytic malignant lymphoma.

In the normal intestinal mucosa there is a histologic "gap" between germinal center cell activity and extrafollicular plasma cell proliferation which can be explained by Parrot (1976) suggestion that the antibody forming cell precursors from the follicle center (Peyer's patch) enter the circulation before "homing" to the gut lamina propria where they appear as plasma cells. In our case, the connection between germinal center cells and mature-looking plasma cells is based on direct evidence, i.e. on the intrafollicular maturation of antibody producing precursor cells to plasma cells in some of the neoplastic follicles. These intrafollicular plasma cells belong to the same abnormal alpha chain positive/light chain negative plasma cell population which infiltrates the lamina propria and also the muscularis propria. Occasional centrocytes of neoplastic germinal centres which do not show plasmacytic tansformation are similarly alpha chain positive/light chain negative.

The relation between follicular center cells and the sarcomatous appearing pleomorphic cell proliferation is more difficult to substantiate by immunohistology. The abnormal immunoblast-like cells and the majority of Sternberg-Reed type giant cells fail to react with antisera to any class of immunoglobulins. Occasional Sternberg-Reed type cells are weakly alpha chain positive. It appears likely that these are degenerative forms which have taken up alpha heavy chain protein nonspecifically. The mature looking plasma cells in the pleomorphic proliferation are partly abnormal alpha chain positive/light chain negative cells but a number of gamma chain positive/light chain positive cells can be identified among them.

The actual manifestation of a neoplastic change in alpha heavy chain disease cannot be confirmed by the immunohistological demonstration of light chain monotypia because of the failure of light chain synthesis (Seligmann et al. 1969; Buxbaum and Preud'homme 1972). One must rely on histopathological signs of malignancy. Our observations suggest that the neoplastic transformation takes place in the germinal centres. Follicular lymphoma may result from a multifocal neoplastic transformation of germinal centres or reflect selective migration and homing of the neoplastic cells to B-cell zones. This interpretation concurs with Isaacson's (1979) opinion that discrete foci of follicular centre cell lymphoma of centroblastic/centrocytic type can be detected as the earliest sign of invasive tumor. The evolution of MTL seems to begin with centroblastic/centrocytic lymphoma of low grade malignancy and take a similar course of progression to high grade malignancy as the lymph node – based cases.

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References

Bonomo L, Dammacoo F, Marano R, Bonomo GM (1972) Abdominal lymphoma and alpha chain disease. Am J Med 52:73–86

Buxbaum JN, Preud'homme JL (1972) Alpha and gamma heavy chain diseases in man: intracellular origin of the aberrant polypeptides. J Immunol 109:1131–1137

Curran RC, Gregory J (1978) Demonstration of immunoglobulin in cryostat and paraffin sections of human tonsil by immunofluorescence and immunoperoxidase techniques. J Clin Pathol 31:974–983

Eidelmann S, Parkins R, Rubin CE (1966) Abdominal lymphoma presenting as malabsorption. A clinico-pathological study of nine cases in Israel and a review of literature. Medicine (Balt.) 45:111–137

Franklin EC, Lowenstein J, Bigelow B, Metzer M (1964) Heavy chain disease. A new disorder of serum gamma-globulins. Report of the first case. Am J Med 37:332–350

Gérard-Marchant R, Hamlin I, Lennert K, Rilke F, Stansfeld AG, van Unnik JAM (1974) Classification of non-Hodgkin's lymphomas. Lancet II:406–408

Isaacson P (1979) Middle East lymphoma and alpha-chain disease: an immunohistochemical study. Am J Surg Pathol 3:431–441

Isaacson P (1981) Primary gastrointestinal lymphoma Virchows Arch [Pathol Anat] 391:9–31

Isaacson P, Wright DH, Judd MA, Jones DB, Payne SV (1980) The nature of the immunoglobulin-containing cells in malignant lymphoma: An immunoperoxidase study. J Histochem Cytochem 28:761–770

Lechago J, Sun NCJ, Weinstein WM (1979) Simultaneous visualization of two antigens in the same tissue section by combining immunoperoxidase with immunofluorescence techniques. J Histochem Cytochem 27:1221–1225

Lennert K, Mohri N (1978) Histopathology and diagnosis of non-Hodgkin's lymphomas. In: Lennert K (ed) Malignant lymphomas other than Hodgkin's disease. Springer, Berlin, Heidelberg, New York, pp 111–469

Lewin JJ, Kahn LB, Novis BH (1976) Primary intestinal lymphoma of "Western" and "Mediterranean" type, alpha chain disease and massive plasma cell infiltration. Cancer 38:2511–2528

Lukes RJ, Collins RD (1974) Immunologic characterization of human malignant lymphomas. Cancer 34:1488–1503

Lukes RJ, Parker JW, Taylor CR, Tindle BH, Cramer AD, Lincoln TL (1978) Immunologic approach to non-Hodgkin's lymphomas and related leukemias. Analysis of the results of multiparameter studies of 425 cases. Semin Hematol 15:322–351

Mepham BL, Frater W, Mitchell BB (1979) The use of proteolytic enzymes to improve immunoglobulin staining by the PAP technique. Histochem J 11:345–347

Nathwani BN, Kim H, Rappaport H, Solomon J, Fox M (1978) Non-Hodgkin's lymphomas. A clinicopathologic study comparing two classifications. Cancer 41:303–347

Osserman EF, Takatsuki K (1964) Clinical and immunological studies of four cases of heavy (H-gamma 2) -chain disease. Am J Med 37:351–373

Parrot DMV (1976) The gut as a lymphoid organ. Clin Gastroenterol 5:211–228

Rambaud JC, Bognel C, Prost A, Bernier JJ, Quinterec J le, Lambling A, Danon F, Hurez D, Seligmann M (1968) Clinicopathological study of a patient with "Mediterranean" type lymphoma and a new type of IgA abnormality (alpha chain disease). Digestion 1:321–336

Rambaud JC, Matuchansky O (1973) Alpha-chain disease. Lancet I:1430–1432

Rambaud JC, Modigliani R, Ngvyen Phuoc BK, Le Carrer M, Mehant M, Valleur P, Galian A, Danon F (1980) Non-secretory alpha-chain disease in intestinal lymphoma. N Engl J Med 303:53

Ramot B, Shahin N, Bubis JJ (1965) Malabsorption syndrome in lymphoma of small intestine. A study of 13 cases. Isr J Med Sci 1:221–226

Rappaport H (1966) Tumors of the hematopoietic system. In: Atlas of tumor pathology. Sect 3, Fasc 8. Armed Forces Institute of Pathology, Washington DC

Rappaport H, Ramot B, Hulu N, Park JK (1972) The pathology of so-called Mediterranean abdominal lymphoma with malabsorption. Cancer 29:1502–1511

Seligmann M (1975) Alpha chain disease. Immunoglobulin abnormalities, pathogenesis and current concepts. Br J Cancer 31:Suppl II 356–361

Seligmann M, Danon R, Hurez D, Mihaesco E, Preud'homme JL (1968) Alpha chain disease: a new immunolgobulin abnormality. Science 162:1396–1397

Seligmann M, Mihaesco E, Hurez D, Mihaesco C, Preud'homme JL, Rambaud JC (1969) Immunochemical studies in four cases of alpha chain disease. J Clin Invest 48:2374–2389

Seligmann M, Rambaud JC (1969) IgA abnormalities in abdominal lymphoma (alpha chain disease) Isr J Med Sci 5:151–157

Shahid MJ, Alami SI, Nassar VH, Balikian J, Salem AA (1975) Primary intestinal lymphoma with paraproteinaemia. Cancer 35:848–858

Tabbane S, Tabbane F, Cammoun M, Moural N (1976) Mediterranean lymphomas with alpha heavy chain monoclonal gammopathy. Cancer 38:1898–1996

World Health Organisation (1976) Alpha-chain disease and related small intestinal lymphoma: A Memorandum. Bulletin No 54:615–624

Zlotnik A, Levy M (1974) Alpha heavy chain disease – A variant of Mediterranean lymphoma. Arch Intern Med 128:432–436

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