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Editorial

Primary Gastrointestinal Lymphoma

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Summary. Despite the fact that the gastrointestinal tract is the commonest site of extranodal malignant lymphoma, gastrointestinal lymphomas remain poorly characterised. Attempts to fit gastrointestinal lymphoma into the newer classifications have been hampered by its relative rarity (at least in "Western" countries) and the poor fixation of specimens which so often bedevils gastrointestinal pathology as a whole. Apart from the overall classification there are two other aspects of gastrointestinal lymphoma that are of particular interest. These are the nature of the intestinal lymphoma that occurs as a complication of coeliac disease and the gastrointestinal lymphomas that occur so commonly in the Middle East. As newer techniques have begun to be applied to gastrointestinal lymphomas a measure of agreement over their classification is emerging. Controversy continues, however, over coeliac disease associated lymphoma particularly with regard to the recently described entity of malignant histiocytosis of the intestine. Interest in gastrointestinal lymphoma, which occurs with such high frequency in the Middle East, is directed principally at the entity called Mediterranean lymphoma which is characterised by malabsorption and plasma cell infiltration of the intestinal lamina propria. In some of these cases α-heavy chain paraprotein is present in the serum or duodenal juice. There is considerable debate as to whether the plasma cell infiltrate is itself neoplastic and also as to the nature of the lymphoma that evolves in this setting. A great deal of work remains to be done in the field of gastrointestinal lymphoma with particular reference to coeliac disease and α-chain disease. Morphological studies alone are insufficient and the application of newer techniques is essential if we are to increase our understanding of this important group of diseases.

Key words: Lymphoma – Gastrointestinal lymphoma – Coeliac disease – α-chain disease

In 1932 Ullman and Abeshouse introduced their paper on lymphosarcomas of the small and large intestines with the following paragraph:

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"A search of the literature on the subject of lymphosarcoma of the intestines reveals a marked diversity of opinion concerning its morphology, histogenesis and etiology. This state of affairs is further complicated by the lack of any uniform nomenclature. As Ewing pointed out there has prevailed for many years an inadequate clinical classification of lymphoid tumors".

Writing nearly 25 years later Marshall (1956) summed up the position more succintly "Unfortunately in some diseases of the reticular tissues it is impossible to state in general terms, on a single examination of the lesions alone, either what they are or what they are not".

The wide acceptance of the Rappaport classification of malignant lymphoma introduced in 1966 and the recent refinements of this by the Kiel group (Gerard-Marchant et al. 1974) and Lukes and Collins (1974) has done much to clarify the confusion surrounding the classification of non-Hodgkin's nodal lymphomas but the comments of Ullman and Abeshouse and Marshall remain almost as pertinent to gastrointestinal lymphoma today as they were in 1932, despite the fact that the gastrointestinal tract is the commonest site of extranodal lymphoma. The reasons for this are to be found partly in the relative rarity of gastrointestinal lymphoma, at least in the developed countries, and partly in the frequency with which both surgical and post-mortem material suffer from poor fixation. Yet another problem is the exact definition as to what constitutes primary gastrointestinal lymphoma since nodal lymphoma tends to involve the gastrointestinal tract when it disseminates. Dawson et al. (1961) established strict criteria for the diagnosis of primary gastrointestinal lymphoma which have been well accepted but which are somewhat restrictive particularly with regard to the requirement that liver and splenic (and bone marrow) involvement be absent. Certain lymphomas (e.g., follicular lymphomas of centroblastic/centrocytic type) are characteristically widely disseminated at diagnosis but are commonly accepted as arising in the lymphoid tissue in which they present clinically since, in some instances at least, they are confined to the presenting area. For practical purposes cases can be accepted as examples of primary gastrointestinal lymphoma when the gastrointestinal lesion has been the presenting focus of disease necessitating the direction of treatment primarily to that site. Staging procedures, not in vogue at the time Dawson et al. established their criteria, might reveal microscopic involvement of liver and spleen or other areas but the likelihood remains that the disease started in the gastrointestinal tract and many of the cases are indeed localized there. Cases presenting with tumour in lymphoid tissue outside the gastrointestinal tract which have involved the gastrointestinal system late in their course, sometimes massively, should not be included.

There are three aspects of gastrointestinal lymphoma that are of special interest. The first is to establish just how these tumours fit into the new lymphoma classifications which have followed recent advances in the understanding of lymphoproliferative disease. Techniques such as those described by Otto et al. in their study reported in this issue of the Archiv have done much to develop these newer concepts but have been applied only rarely to isolated cases or series of cases of gastrointestinal lymphoma (Isaacson et al. 1979; Watanabe et al. 1980). The second relates to the association between gastrointestinal lymphoma and coeliac disease. While this association is undoubted (Barry and Read 1973; Harris et al. 1967; Holmes et al. 1976) the histopathology of

the lymphoma itself has been poorly studied and it is clearly of some importance to establish whether this type of lymphoma is a specific histopathological entity or whether the association represents a greater susceptibility to lymphoproliferative disease as a whole. Finally, it is now widely appreciated that gastrointestinal lymphoma is an extremely common disease in the Middle East where it is often associated with malabsorption and α-heavy chain disease. The histopathology of these tumours is also poorly characterised and their relationship to the newer lymphoma classifications and thus to gastrointestinal lymphoma as it occurs in the West is poorly understood.

Early accounts of gastrointestinal lymphoma such as that of Ullman and Abeshouse made use of classifications of lymphoid tumours which bear very little relevance to those in use today. Furthermore, from the illustrations and histological descriptions it is impossible to fit the cases even into broad histological categories comparable to those now recognised. An additional confusing factor is the inclusion in these early studies of many cases of primary nodal lymphoma involving the gastrointestinal tract secondarily. The earliest series of gastrointestinal lymphomas that can usefully be compared with those of today is that of Faulkner and Dockerty (1952) who used the classification of Gall and Mallory (1942). In broad terms these authors described 56% of their 33 cases as clasmacytic or stem cell (large cell) lymphoma, 33% as lymphocytic (small cell) lymphoma and 11% as examples of Hodgkin's disease. The lymphocytic lymphomas, 1 of which was follicular, probably represented follicular centre cell tumours and an equally high percentage of this type of lymphoma has characterised all subsequently published series (Henry and Farrer-Brown 1977; Isaacson et al. 1979; Lewin et al. 1978; Loehr et al. 1969; Naqvi et al. 1969). It is now clear that Hodgkin's disease is a very rare primary tumour of the gastrointestinal tract and the cases featuring in earlier series either represent secondary involvement or have been misdiagnosed. Lymphoblastic lymphomas such as those included by Otto et al. in their current paper feature to a greater or lesser extent in the various series and this variation is accounted for by differences in the number of paediatric cases included since this tumour is commonest in childhood. There is, then, considerable agreement on the nature of many gastrointestinal lymphomas, but this agreement is often obscured by the clouds of controversy surrounding the nature of the lymphomas composed of larger cells, the 'histiocytic' lymphomas of Rappaport. While a substantial proportion of these are likely also to be follicle centre cell derived B-cell neoplasms this group of tumours continues to provoke discussion, much of which is centered around two principal controversies. The first of these arises from the high incidence of gastrointestinal plasmacytomas (39%) reported by Henry and Farrer-Brown, many of which were large cell tumours. These authors did not substantiate the plasmacytic nature of the cells with immunohistochemical techniques such as those used subsequently by Isaacson et al. and described by Otto et al. in their current paper. It should be stressed that to interpret a malignant lymphoma as showing plasmacytic or plasmacytoid differentiation solely on the basis of routine paraffin sections is unreliable, a common cause of a plasmacytoid appearance in malignant lymphomas being artefact induced by poor fixation. It is doubtful that as many as 39% of gastrointestinal lympho-

mas are plasmacytomas but it nevertheless must be conceded that the definition of plasma cell varies and it is conceivable that the cases classified as immunocytomas and immunoblastic sarcomas by Otto et al. would be acceptable to some as plasmacytomas if the definition of plasmacytic differentiation were to rest on cytoplasmic immunoglobulin (Ig) synthesis alone. It has, however, recently been shown that follicle centre cells (i.e., centroblasts and centrocytes) can synthesise cytoplasmic Ig and that most of the cells in malignant lymphomas shown to synthesise cytoplasmic Ig are in fact centrocytes and centroblasts and not plasma cells or immunoblasts (Isaacson et al. 1980). The majority of the tumours in the series of Otto et al. are therefore probably of follicle centre cell origin.

There remains the controversy surrounding histiocytic (i.e. monocyte/macrophage) derived tumours of the gastrointestinal tract. Isaacson et al. (1979) have suggested that a significant number of primary gastrointestinal lymphomas are of true histiocytic derivation. In their study, which was the first to apply immunohistochemical and plastic sectioning techniques to a large series of gastrointestinal lymphomas, polytypic staining (i.e., k and λ light chain) of tumour cells was held to be the chief criterion of their histiocytic nature. Subsequent studies by the same authors have shown that while histiocytes may indeed take up polytypic Ig (particularly IgG) from their environment, polytypic staining alone is insufficient evidence of the histiocytic nature of a lymphoreticular neoplasm (Isaacson and Wright 1979). Positive staining for lysozyme is good evidence of the histiocytic nature of tumour cells but interpretation of this stain is difficult since positive staining is dependent on tumour cell differentiation and it can be difficult to distinguish between reactive histiocytes and malignant histiocytes many of which do not stain positively (Risdall et al. 1980). On these grounds the classification of the group of histiocytic lymphomas (11 cases) in the series reported by Isaacson et al. can be criticised. The majority of the histiocytic tumours (22 cases) in this series were, however, examples of malignant histiocytosis of the intestine and the evidence for the true histiocytic nature of this group of tumours is much more concrete and will be discussed later.

Although an association between the malabsorption syndrome and gastrointestinal lymphoma was first reported in 1937 (Fairley and Mackie) few of the subsequent reviews of gastrointestinal lymphoma as a whole placed any emphasis on this association. This extends even to recent publications with no mention of villous atrophy, malabsorption or coeliac disease in the review of Henry and Farrer-Brown and the citing of only 2 cases with malabsorption (not including cases of Mediterranean lymphoma) in the series of Lewin et al. Exceptions are the series of Isaacson et al. and the present series reported by Otto et al. Fairley and MacKie and subsequent authors (Sleisenger et al. 1953; Scudamore 1961; Eakins et al. 1964) were of the view that it was the intestinal lymphoma that was responsible for the malabsorption but following the development of peroral jejunal biopsy it became clear that the reverse was true and that intestinal lymphoma occurred as a complication of preceding malabsorption (Gough et al. 1967). The jejunal mucosa in these cases showed villous atrophy, crypt hyperplasia, plasmacytosis of the lamina propria and increased intraepithelial lymphocytes. This lesion is identical to that of coeliac disease and although not totally

proven it is highly likely that the malabsorption which is complicated by intestinal lymphoma is coeliac disease (i.e., gluten sensitive enteropathy). The minimum evidence required to show that a case of intestinal lymphoma falls into this group is the demonstration in the jejunal mucosa uninvolved by tumour of villous atrophy, crypt hyperplasia, and the other changes described above (Cooke and Asquith 1974). Response of this lesion to a gluten-free diet is definitive evidence of coeliac disease (although some would insist on demonstration of recurrence of the lesion following gluten challenge). Isaacson and Wright (1980) have reviewed 39 such cases and after detailed clinical, morphological and immunohistochemical studies have concluded that the lymphoma complicating coeliac disease is of uniform histogenesis being monocyte/macrophage derived. Because of the morphological similarity to the entity known as malignant histiocytosis (histiocytic medullary reticulosis) (Byrne and Rappaport 1973; Scott and Robb-Smith 1939) they have called this tumour malignant histiocytosis of the intestine (MHI). Among the features of this disease pertinent to the cases of coeliac disease associated lymphoma included in the series of Otto et al. are the invariable demonstration of jejunal villous atrophy, the late age of onset, the distinctive morphological and immunohistochemical characteristics of the tumour and the high incidence and distinctive pattern of dissemination. In common with other published series of coeliac disease associated lymphoma, notably those of Holmes et al. (1976) and Freeman et al. (1977), the disease occurred in the 5th to 7th decade with only an occasional younger patient, the youngest being 43. The histological appearances varied markedly from monomorphic infiltrates of mature recognisable histiocytes to infiltrates of immature cells resembling immunoblasts. Other cases showed marked pleomorphism with multinucleated giant cells bearing a superficial resemblance to Reed-Sternberg cells. Plastic sections, electron microscopy and, in 3 cases, histochemistry were all consistent with the histiocytic nature of the cells and phagocytosed red cells and other material was present in many cases. Spread to lymph nodes, liver, spleen and bone marrow was the rule with phagocytic malignant histiocytes in the marrow a common finding. Immunohistochemical findings included intracytoplasmic polytypic Ig (especially IgG) in a proportion, but not all, of the cases, the absence of J chain in these cells providing further evidence that the presence of this immunoglobulin represented uptake rather than synthesis (Isaacson 1979b). While lysozyme was detected inconstantly an almost invariable finding was the presence of αl-antitrypsin within the cells. This substance, which is synthesised by monocytes, has not been detected in benign or malignant lymphoreticular cells of B or T lymphocyte lineage and appears to be a reliable histiocytic marker (Isaacson et al. 1979). The characterisation of MHI and its unique association with jejunal villous atrophy is of considerable biological and epidemiological interest.

How then are we to reconcile the findings of Otto et al. described in this issue of the Archiv with those of Isaacson and Wright. It is a pity that the appearance of uninvolved jejunal mucosa is not illustrated in any of the cases. With an age range of 27–41 the patients are unusually young for this disease especially when compared with the other non-coeliac cases (excepting cases of lymphoblastic lymphoma) which fall into the older age group characteristic

of intestinal lymphoma. The immunohistochemical findings too, are at variance with those of Isaacson and Wright and perhaps this discrepancy could be resolved by extending the range of antigens studied to include J chain and α1-antitrypsin. It is hoped that the controversy surrounding MHI and its association with coeliac disease will be further clarified by a nationwide investigation into coeliac disease associated malignancy currently in progress under the auspices of the Clinical Research Council of Great Britain.

No discussion of gastrointestinal lymphoma would be complete without a comment on the disease as it occurs in the Middle East. The extraordinarily high incidence of gastrointestinal lymphoma in the Middle East has been recognised since 1963 when Frand and Ramot noted a high incidence of this disease in non-Ashkenazi Jews and Arabs in Israel. Many of these cases are associated with malabsorption but it should be stressed that the malabsorption is not due to gluten sensitivity (Eidelman et al. 1966). Many of the cases of gastrointestinal lymphoma in the Middle East are histologically similar to those occurring in Western countries (Al-Saleem and Zardawi 1979), lymphoblastic lymphoma being common in the paediatric age group and follicle centre cell lymphomas occurring in adult patients. Among the large numbers of gastrointestinal lymphomas occurring in the Middle East an as yet undefined proportion is characterised by malabsorption and a diffuse mature plasmacytic infiltrate in the lamina propria of the intestine. To this group the terms Mediterranean lymphoma or IPSID (immunoproliferative disease of the small intestine) have been applied (Revue Generale 1976; World Health Organisation 1976). Confusion has arisen from the indiscriminate use of the terms Mediterranean lymphoma and IPSID to include all cases of gastrointestinal lymphoma occurring in the Middle East and it must be stressed that these terms apply only to those cases with the clinical and histological features mentioned above (Rambaud, J.C., personal communication). In some, but not all, cases of Mediterranean lymphoma abnormal α-heavy chains have been detected in the serum and duodenal juice giving rise to the term α-chain disease (Rambaud et al. 1968). The detection of this α-heavy chain paraprotein can be difficult but immunohistochemical staining can detect the surfeit of α-chain positive plasma cells in the lamina propria and the deficit or near absence of cells containing light chains (Isaacson 1979a). Using this method it should be possible to establish whether all cases of Mediterranean lymphoma occur in a setting of α-chain disease which, in some instances, may be of a non-secretory nature (Rambaud et al. 1980). It is as yet uncertain whether the mature plasma cell infiltrate in these cases represents a neoplastic condition or not. While the monoclonality, and hence neoplastic nature, of the plasma cell infiltrate is suggested by the uniform synthesis of α-heavy chains proof that all cells are of the same idiotype is lacking since the α-heavy chain produced lacks the variable region of the normal α-chain molecule (World Health Organisation 1976). The mechanism by which overt lymphoma evolves is unclear and there is some disagreement over the nature of this lymphoma. Some workers (Galian et al. 1977) suggest that an immunoblastic sarcoma gradually evolves from the α-chain synthesising plasma cells while others (Isaacson 1979a) suggest that discrete foci of follicular centre cell lymphoma of centroblastic/centrocytic type can be detected as the earliest sign of invasive tumour.

The striking geographic variability of gastrointestinal lymphoma, its various histological characteristics and its association with coeliac disease are all fruitful areas for investigation. The collection of large series of cases by centralised institutions with access to newer immunological techniques should be encouraged if we are to increase the understanding of this enigmatic group of tumours. Morphologic studies alone will not increase our understanding of these lymphomas especially if they continue to be performed on poorly fixed material. There is a particular need for careful studies of large series of intestinal lymphoma associated with coeliac disease and α-chain disease for it is likely that intensive studies of these two diseases will reveal information relevant to the aetiology and pathogenesis of lymphoreticular malignancy as a whole.

References

Al-Saleem T, Zardawi IM (1973) Primary lymphomas of the small intestine in Iraq. Histopathology 3:89–106

Barry RE, Read AE (1973) Coeliac disease and malignancy. Q J Med 42:665–675

Byrne GE, Rappaport H (1973) Malignant histiocytosis. In: Akazaki K, Rappaport H, Berard CW, et al. (eds) Gann Monograph on Cancer Research vol 15. Tokyo

Cooke WT, Asquith P (1974) Introduction and definition of coeliac disease. Clin Gastroenterol 3:3–10

Dawson IMP, Cornes JS, Morson BS (1961) Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 49:80–89

Eakins D, Fulton T, Hadden DR (1964 Reticulum cell sarcoma of the small bowel and steatorrhoea. GUT 5:315–323

Fairley NH, Mackie FP (1937) The clinical and biochemical syndrome in lymphadenoma and allied diseases involving the mesenteric lymph glands. Br Med J 1:3972–3980

Faulkner JW, Dockerty MB (1952) Lymphosarcoma of the small intestine. Surg Gynecol Obstet 95:76–84

Frand V, Ramot B (1963) Malignant lymphoma: an epidemiological study. Harefugh 65:83–86

Freeman HJ, Weinstein WM, Shnitka TK, Piercey JRA, Wensel RH (1977) Primary abdominal lymphoma. Presenting manifestation of celiac sprue or complicating dermatitis herpetiformis. Am J Med 63:585–594

Galian A, Lecestre M-J, Scotto J, Bognel C, Matuchansky C, Rambaud J-C (1977) Pathological study of alpha-chain disease, with special emphasis on evolution. Cancer 39:2081–2101

Gall EA, Mallory TB (1942) Malignant lymphoma. A clinicopathologic survey of 618 cases Am J Pathol 18:381–415

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

Gough KR, Read AE, Naish JM (1962) Intestinal reticulosis as a complication of idiopathic steatorrhoea. GUT 3:232–239

Harris OD, Cooke WT, Thompson H, Waterhouse JAH (1967) Malignancy in adult coeliac disease and idiopathic steatorrhoea. Am J Med 42:899–912

Henry K, Farrer-Brown G (1977) Primary lymphomas of the gastrointestinal tract. I: Plasma cell tumours. Histopathology 1:53–76

Holmes GKT, Stokes PL, Soraham TM, Prior P, Waterhouse JAH, Cooke WT (1976) Coeliac disease, gluten-free diet and malignancy. GUT 17:612–619

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

Isaacson P (1979b) Immunochemical demonstration of J-chain: a marker of B-cell malignancy. J Clin Pathol 32:802–807

Isaacson P, Wright DH (1979) Anomolous staining patterns in immunohistologic studies of malignant lymphoma. J Histochem Cytochem 27:1197–1199

Isaacson P, Wright DH (1980) Malabsorption and intestinal lymphomas. In: Wright R (ed) Recent adavances in gastrointestinal pathology, chapter 12. WB Saunders Company Ltd., London

Isaacson P, Jones DB, Judd M (1979) αl-antitrypsin in human macrophages. Lancet ii:964–965

Isaacson P, Wright DH, Judd MA, Mepham BL (1979) Primary gastrointestinal lymphomas: A classification of 66 cases. Cancer 43:1805–1819

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

Lewin KJ, Kahn LB, Novis BH (1976) Primary intestinal lymphoma of "Western" and "Mediterranean" type, Alpha-chain disease and massive plasma cell infiltration. A comparative study of 37 cases. Cancer 38:2511–2528

Loehr WJ, Mujahed Z, Zahn FD, Gray GF, Thorbjarnarson B (1969) Primary lymphoma of the gastrointestinal tract. A review of 100 cases. Ann Surg 2:232–238

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

Marshall AHE (1956) An outline of the cytology and pathology of the reticular tissue. Charles C Thomas, Springfield, Illinois

Naqvi MS, Burrows L, Kark AE (1969) Lymphoma of the gastrointestinal tract. Prognostic guides based on 162 cases. Ann Surg 2:221–231

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

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

Rappaport H (1966) Tumors of the hemopoietic system. In: Atlas of tumor pathology, section 3 fasicle 8. US Armed Forces Institute of Pathology, Washington DC

Revue Générale (1976) Alpha-chain disease and related small intestinal lymphoma. Report of a WHO meeting of investigators. Arch Fr Mal App Dig 65:591–607

Scudamore HH (1961) Observations on secondary malabsorption syndromes of intestinal origin. Regional enteritis, lymphoma, jejunal diverticulosis, gastrojejunocolic fistula. Ann Intern Med 55:433–447

Sleisenger MH, Almy TP, Barr DP (1953) The sprue syndrome secondary to lymphoma of the small bowel. Am J Med 15:666–674

Ullman A, Abeshouse BS (1932) Lymphosarcoma of the small and large intestines. Ann Surg 95:878–915

Watanabe S, Hirota T, Shimosato Y, Ibo A, Zeze F, Hojo K (1980) Unusual histiocytic tumor of the small intestine. Hum Pathol 11:289–293

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

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