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CASE REPORT

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Early malignant histiocytosis of the intestine: an autopsy report

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Abstract A 63-year-old man with malignant histiocytosis of the intestine died 3 days after gastrectomy for early gastric adenocarcinoma. Malignant histiocytosis of the intestine was unexpectedly found at autopsy. The intestine was thickened with mucosal erosions. Histologically, a few atypical large histiocyte-like cells were found in focal aggregates in the mucosa. These large cells expressed the T-cell antigen and monoclonality was demonstrated by the polymerase chain reaction showing variable-joining segment rearrangement in the T-cell receptor delta-chain gene. Malignant histiocytosis of the intestine was thus diagnosed.

Key words Autopsy
Early malignant histiocytosis of the intestine
Cell clonality · Polymerase chain reaction

Introduction

Malignant histiocytosis of the intestine (MHI) was recognized as a specific histopathological entity by Isaacson and Wright in 1978 (Isaacson and Wright 1978a, b). Because of the morphology and positivity of alpha-1-antitrypsin, this tumour was considered to originate in histiocytes (Isaacson and Jones 1983). Recently rearrangement of the T-cell receptor (TCR) β-chain gene and immunocytochemistry have demonstrated a T-lymphocyte phenotype and genotype (Isaacson et al. 1985).

The increased incidence of MHI in patients with coeliac disease is well recognized (Swinson et al. 1983). It can be extremely difficult to diagnose MHI before acute abdominal episodes often related to perforation, and diagnostic laparotomy may not be informative (Mead et al. 1987).

Rearrangement of antigen receptor genes and monoclonality of a small cell population can be detected by the polymerase chain reaction (PCR; MacCarthy et al. 1990; Trainor et al. 1990, 1991) and we used this method to examine tissue from an autopsy patient with early MHI who died following surgery for early gastric cancer.

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Case report

A 63-year-old Japanese man was admitted to Fukuoka University Hospital to undergo a gastrectomy. He had recently had epigastric pain, but no other systemic or gastrointestinal symptoms. Barium examination revealed a small lesion in the stomach, but no lesion in the intestine. The findings of endoscopy and biopsies revealed early gastric cancer in the stomach. All laboratory findings on admission were within normal limits. Hypotension, respiratory failure, and acidosis developed suddenly after the operation and they were never satisfactorily reversed. The patient died 3 days after surgery. An autopsy was performed.

Materials and methods

Immunostaining was performed with L26 for B-cells and kappa, lambda, IgG, IgM, IgA, and IgD antibodies (Dakopatts, Glostrup, Denmark); with UCHL-1, MT-1 and OPD-4 for T-cells (Dakopatts and Beckton-Dickinson, Mountain View, Calif.); with KP-1, LeuM1, alpha-1-antitrypsin and lysozyme for monocytes (Dakopatts and Beckton-Dickinson); with BM-1 for granulocytes (Dakopatts); with common leucocyte antibody (CLA) for leucocytes (Dakopatts); and with BerH2, epithelial membrane antigen (EMA), and proliferating cell nuclear antigen (PCNA) for proliferating cells (Dakopatts).

For PCR we deparaffinized the sections and digested them with protease K for 7 days. Specific primers were synthesized on the basis of the published DNA sequence. Consensus primers used to amplify the immunoglobulin heavy chain variable region (VH) an joining region (JH) were primer VH: CTGTCGACACGGCCGTGTATTACT and primer JH: AACTGCAGAGGAGACGGTGAC, synthesized in correspondence with V and J regions

(McCarthy et al. 1990). The primers for amplification of the TCR β 1 chain diversity region (D) and J region were primer D β 1: CCCATGGGAGGGGCTGTTTTTG and primer J β 1: CCCGAGTCAAGAGTGGAGCC; for β 2 chain we used primer D β 2: GTATCATGGTGTAACATTGTGGGG, primer J β 2: AAGGTGGGGAGACGCCCGAAT, synthesized in correspondence with D and J regions (Toyonaga et al. 1985). The primers for TCR δ were V δ: AAAGTGGTCGCTATTCTGTC, and J δ: TGGTTCCACAGTCACACGGG (MacIntyre et al. 1989). For Epstein-Barr virus (EBV), primer EBW-1: CCAGAGGTAAGTGGACTT, primer EBW-2: GACCGGTGCCTTCTTAGG, and probe EBW: TTCTGCTAAGCCCAC were synthesized, to correspond to the *Bam*HI W region of EBV (Saito et al. 1989). For human T-cell leukaemia virus type I (HTLV-1), primer pX-1: ATGCTGTTTCGCCTTCTCAG, and primer pX-2: TAAGGACCTTGAGGGTCTTA were synthesized to correspond to the pX region of HTLV-I (Seiki et al. 1983). We used the HTLV-I full-length probe. For amplification we used with the GeneAmp DNA amplification reagent kit and DNA Thermal Cycler (Perkin-Elmer Cetus, Norwalk, Conn., USA). To exclude non-specific reactions, the perfect-match polymerase enhancer was added (Stratagene, La Jolla, Calif., USA).

Results

Autopsy findings included severe visceral congestion and the small intestine showed severe erosions with pseudomembranous change and mural thickening of the intestinal walls. Surgery revealed early gastric adenocarcinoma, poorly differentiated, localized within the mucosa. Histological examination of the small intestine showed severe congestion, destruction of crypts, and infiltration of lymphocytes and plasmacytes. A few large histiocyte-like cells with oval or indented large vesicular nuclei, distinct small nucleoli, and slightly amphophilic cytoplasm showing minimal atypia were scattered in the mucosal layer. These cells were located focally in the small intestine; there were no nodal or other metastases (Fig. 1).

Immunohistochemical staining of paraffin sections was performed. The large histiocyte-like cells reacted with UCHL-1 and alpha-1-antitrypsin, and weakly with CLA MT-1 and OPD-4, but not with L26, im-

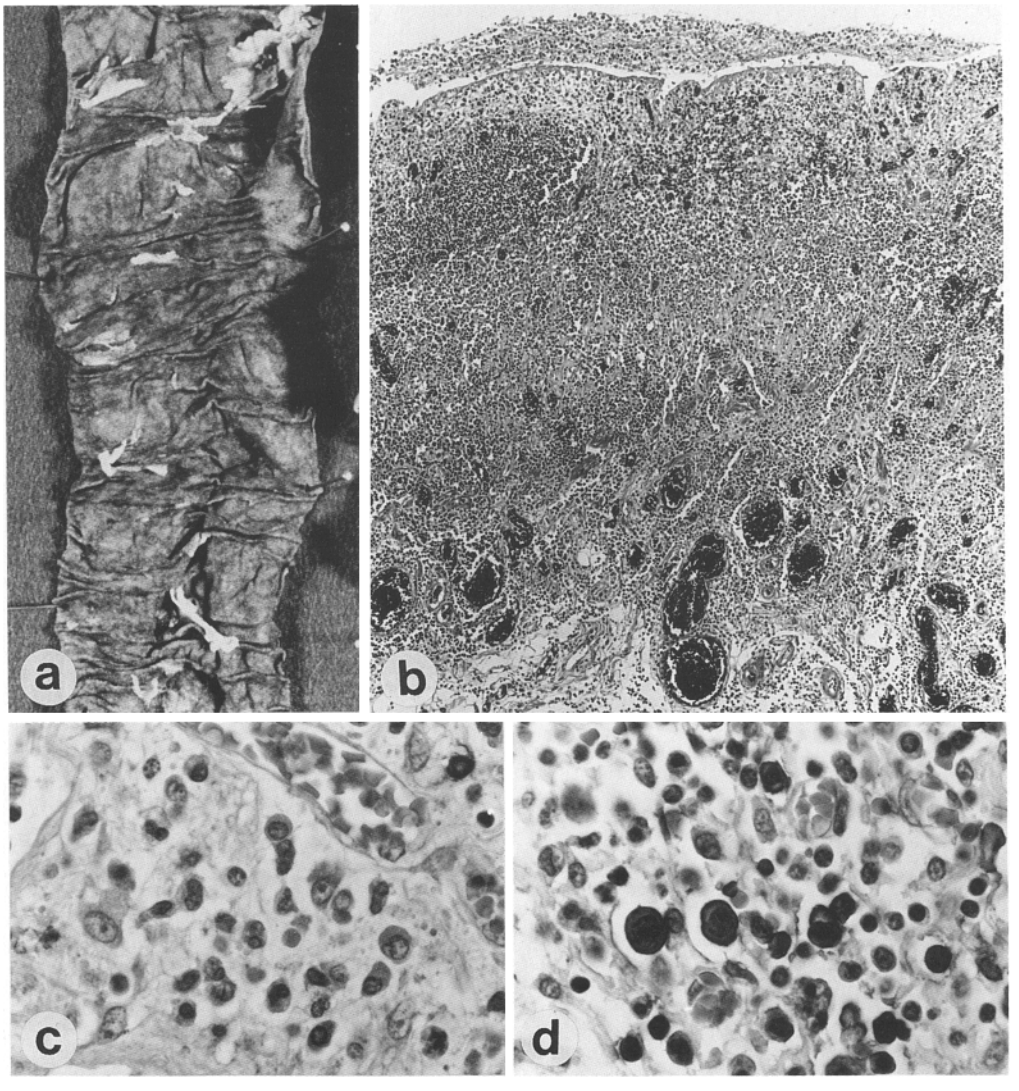

Fig. 1 **a** Small intestine showing erosion with pseudomembranous change. **b** Mucosa showing hypoxic changes with destruction of crypts, inflammatory infiltrates and congestion. **c** Mucosa showing a few scattered large histiocytic cells. **d** Large histiocytic cells reacting with UCHL-1

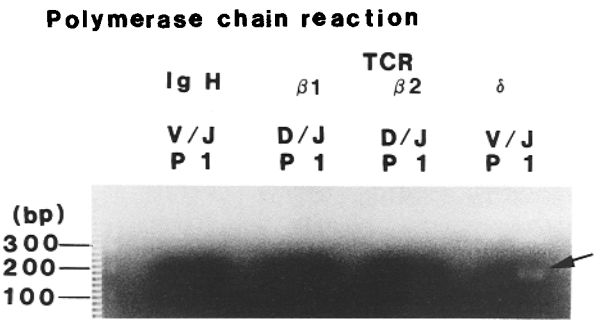

Fig. 2 Only variable (*V*) δ and joining (*J*) δ primers show a clonal band in the intestine at autopsy (*arrow*; *bp* base pairs, *TCR* T-cell receptor, *D* diversity, *IgH* heavy chain, *P* placental DNA)

munoglobulin, KP-1, LeuM1, BerH2, or EMA (Fig. 1). Some large cells expressed PCNA on the nuclei.

In the PCR analysis, TCR δ V-J region showed a monoclonal band, but the TCR β-chain and Ig heavy chain did not (Fig. 2), and there was no amplification of EBV and HTLV-1.

From the results of PCR and immunohistochemistry, the large histiocytic cells were believed to originate in T-lymphocytes.

Discussion

The early histological lesion of MHI has been described by Isaacson, with characteristic lesions consisting of intramucosal histiocytic aggregations that invade both surface and crypt epithelium (Isaacson 1980). The relationship between this disease and coeliac disease is a clear one (Swinson et al. 1983). Series from centers with large numbers of coeliac disease patients suggest that approximately 10% of these patients will develop lymphoma of the small intestine. In another prospective study, 51.4% of the cancer developing in 235 patients with coeliac disease was lymphoma and further review of these cases suggested that approximately 90% were examples of MHI (Swinson et al. 1983). An increase of carcinoma occurring in the pharynx, oesophagus, or small bowel is also documented in patients with coeliac disease (Swinson et al. 1983). The prognosis is poor for MHI patients and late diagnosis, widespread disease, and associated malabsorption are responsible for poor tolerance of chemotherapy (Mead et al. 1987). Radiological examination is not useful in detecting early lesions (Brunton and Guyer 1983).

Our patient complained only of epigastralgia, and had no history of coeliac disease. Histological examination showed a few large histiocytic cells showing minimal atypia in the mucosal layer. On the basis of morphology and positivity of alpha-1-antitrypsin, the tumour cells were believed to originate from histiocytes (Isaacson et al. 1983). However, Stein et al. (1989) reported a group of large-cell lymphomas, positive for alpha-1-antitrypsin and Ki-1, and some with expression of T-cell markers. Later studies showed unequivocally that tumour cells exhibited a T-cell phenotype, sometimes CD3 and especially CD7 (Salter et al. 1986; Salter and Krajewski 1987). This was confirmed by gene rearrangement studies, showing clonal rearrangements of the genes encoding for the β-chain of the TCR in three of four cases studied (Isaacson et al. 1985). A monoclonal antibody (HML-1) has been produced that recognizes the entire intraepithelial lymphocyte population and 50% of lamina propria T-cells, but very few cells outside the mucosa. Immunocytochemistry has shown that all MHIs were positive for HML-1 and that all peripheral T-cell lymphomas and mucosal B-cell lymphomas were negative for that antibody. This strongly suggests that MHI is a tumour of mucosal T-cells, possibly the intraepithelial T-cell component (Spencer et al. 1988). Our case expressed some T-cell antigens UCHL-1, MT-1, and OPD-4, but no monocytic ones. We could not obtain fresh material on which to perform Southern blot analysis.

The sensitivity of the PCR for detecting a monoclonal population admixed in a polyclonal population of blood lymphocytes is approximately 2–5% (Trainor et al. 1991; McCarthy et al. 1992). Thus, the PCR technique is useful in detecting small monoclonal populations. Rearrangement of TCR δ is not confined to T-cell neoplasms; it may also be found in B-cell and myeloid neoplasms (Kimura et al. 1989). In our subject, however, the monoclonal population was demonstrated by the PCR analysis of TCR δ. From the results of PCR and immunochemical staining, the histiocyte-like cells we identified appear to originate in the T-cell clonal population. The methods have proved very useful for diagnosing small clonal populations, and will be useful for biopsy samples.

Mead et al. (1987) have recommended that surgery be used only to establish the diagnosis in the patients with MHI and, where necessary, to correct obstruction or perforation. These patients are poor candidates for extensive surgery, as they are often malnourished and frequently have underlying mucosal abnormalities. Three of nine patients with MHI died within 3 days after laparotomy without symptoms of perforation (Isaacson et al. 1985; Salter et al. 1986).

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