Article is available online at http://www.webio.hu/por/2003/9/3/0188

CASE REPORT

Colliding/Concomitant Tumors of the Intestine: Report of 3 Cases

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Collision/concomitant tumors of the intestine involving lymphomas are very rare. For these cases molecular genetic analyses are valuable diagnostic adjuncts. We report one collision tumor of the rectum (adenocarcinoma and peripheral T-cell lymphoma, unspecified), and two cases of concomitant tumors (carcinoma in the cecum and lymphoma in the ileum; carcinoma in the sigmoid and lymphoma in the ileum). The collision tumor (poorly differentiated adenocarcinoma and a peripheral T-cell lymphoma, unspezified) showed a variable proportion of the anaplastic tumor cells expressing lymphatic markers as well as cytokeratin. Only polymerase chain reaction (PCR) analysis revealing T-cell monoclonality of the anaplastic part of the colliding tumor allowed the correct diagnosis. In the second case, a moderately differentiated adenocarcinoma in the cecum with a concomitant B-cell Non-Hodgkin lymphoma in the ileum, PCR analysis was non contributary. In the third case (adenocarcinoma in the sigmoid colon and a follicular center lymphoma in the ileum) PCR analysis revealed gene rearrangement of the immunoglobulin heavy chain gene. We would like to emphasize that collision and concomitant tumors of the gut are rare and that molecular genetic analysis may be mandatory for correct diagnosis. It is our impression, that these tumors may be diagnosed more often in the intestinal tract if molecular genetic analysis and immunohistochemistry are used routinely, at least for all anaplastic tumors. (Pathology Oncology Research Vol 9, No 3, 188–192)

Keywords: adenocarcinoma, non-Hodgkin lymphoma, colon, ileum

Introduction

Collision tumors and concomitant tumors of the gastrointestinal tract are rare. In some reports the simultaneous occurrence of carcinoids and adenocarcinomas either as collision tumors or as concomitant tumors at different locations[3,4,6,9,13,19] is described. Others describe the simultaneous occurrence of lymphomas – mainly of the mucosa associated lymphoid tissue (MALT) type – together with adenocarcinomas in the stomach in association with *Helicobacter pylori* infection.[10,14,15] Reports about a simultaneous occurrence of non-Hodgkin lymphomas (NHL) and adenocarcinomas in the colon and rectum include a collision tumor in the rectum consisting of an adenocarcinoma and a lymphoma, and a lymphoma in the cecum with a synchronous adenocarcinoma in the sigmoid colon.[1,5,12,18]

We report 3 unusual cases of simultaneous tumors in the gut. The first is a high grade peripheral T-cell lymphoma, unspecified colliding with an adenocarcinoma of the rectum, the second a high grade B-cell NHL in the ileum with an adenocarcinoma of the cecum and the third an adenocarcinoma in the sigmoid colon and a concomitant follicular center lymphoma in the ileum.

Material and Methods

Immunohistochemistry

The specimens were fixed in 5% formaldehyde solution and embedded in paraffin. Sections were routinely stained with hematoxylin and eosin. 5 µm thick sections were immunostained with antibodies (Abs) against: CD2 (YLEM, 1:5), CD3 (DAKO, 1:200), CD4 (YLEM, 1:1),

Received: June 10, 2003; *accepted:* August 25, 2003

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CD5 (NOVOCASTRA, 1:50), CD6 (NEOMARKERS, 1:100), CD7 (NOVOCASTRA, 1:50), CD8 (DAKO, 1:10), CD10 (NEOMARKERS, 1:10), CD20 (DAKO, 1:200), CD21 (DAKO, 1:300), CD23 (BINDING SITE, 1:50), CD30 (DAKO, 1:50), CD43 (DAKO, 1:200), CD45RB (DAKO, 1:10), CD56 (NOVOCASTRA, 1:40), CD57 (DAKO, 1:75), EMA (epithelial membrane antigen) (DAKO, 1:10), pancytokeratin (DAKO, 1:50), bcl-2 (DAKO, 1:10), bcl-6 (DAKO, 1:10), MIB-1 (DAKO, 1:200), kappa light chain (DAKO, 1:100), lambda light chain (DAKO, 1:100). The avidin–biotin complex method was used with prior microwave treatment (160W, 10 min.) as required. The sections were developed with diaminobenzidine and fast red for color development and counterstained with hematoxylin. Double staining was performed with Abs to cytokeratin (pancytokeratin) and CD45RB. For cytokeratin Abs the alkaline phosphatase-anti-alkaline phosphatase (APAAP) method and for the CD45RB Abs the peroxidase-anti-peroxidase staining was used.

In brief, the sections were pretreated with 0,1% protease (type XXIV; Sigma, St. Louis, USA) in phosphate –buffered saline (PBS) for 10 min. at room temperature. For visualization of reaction products sections were treated with 0.02% 3.3´-diaminobenzidine tetrahydrochloride (ph 7.4) yieling a brown colour. In the APAAP method the enzyme reaction was developed with a fast red/naphthol/-As-Bi solution for 45 min at room temperature. The result was a red staining reaction. The incubation time for cytokeratin Abs was 25 min., the incubation time for CD45RB Abs was 30 min..

PCR analysis

Genomic DNA was extracted from formalin-fixed and paraffin-embedded tissues as described elsewhere.[16] Immunoglobulin heavy chain gene and T-cell-receptor gamma chain gene rearrangement were analysed as described previously.[2] PCR products were analysed on 6% polyacrylamide vertical gel electrophoresis.

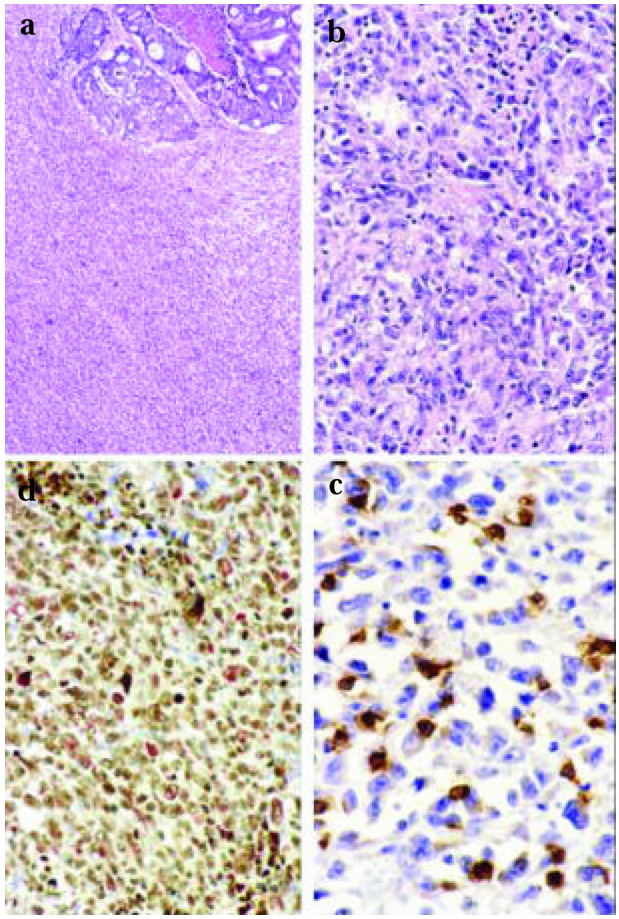

Figure 1. *Case1. Collision tumor in the rectum (peripheral T-cell lymphoma and adenocarcinoma).* ***(a)*** *Moderately differentiated tubular adenocarcinoma colliding with peripheral T-cell lymphoma (H&E).* ***(b)*** *The peripheral T-cell lymphoma shows large blasts with eosinophilic cytoplasm, centrally located nuclei and large nucleoli; the insert shows the tumor cells in higher magnification (H&E).* ***(c)*** *Double staining with Abs to pancytokeratin (red) and CD45RB (brown); few cytokeratin- positive cells are intermingled, most tumor cells react with Abs against CD45RB.* ***(d)*** *Many tumor cells react with Abs against CD8 (a, 40x; b, 100x; insert, 400x; c, 200x; d, 400x).*

Case 1

A 73-year-old male patient was admitted to the hospital with diarrhoea and abdominal pain. Rectoscopy revealed an ulcerated tumor measuring 9 cm in diameter. The patient also had liver lesions suspicious for metastases and an osteolytic lesion in the os sacrum clinically suspicious for multiple myeloma. Two years previously a paraproteinemia of the immunoglobulin kappa light chain type was diagnosed. However, a bone marrow biopsy showed no infiltration by multiple myeloma, a differential blood count was normal.

The colorectal resection specimen contained a tubular adenocarcinoma grade 2 arising in a villous adenoma infiltrating into but not through the muscularis propria. The adenocarcinoma was in continuity with a diffuse infiltrate consisting of non-cohesive medium–sized to large pleomorphic cells and some multinucleated giant cells (*Figure 1a*). The cytoplasm was eosinophilic, the centrally located vesicular nuclei contained coarse chromatin and one or multiple large nucleoli (*Figure 1b, Figure 1b insert*). There was a clear demarcation between the adenocarcinoma located within the inner layers of the gut and the anaplastic tumor component infiltrating the outer layers and the pericolic fat. The adenocarcinoma strongly expressed cytokeratin and EMA. The anaplastic tumor contained several intermingled cytokeratin-positive cells,

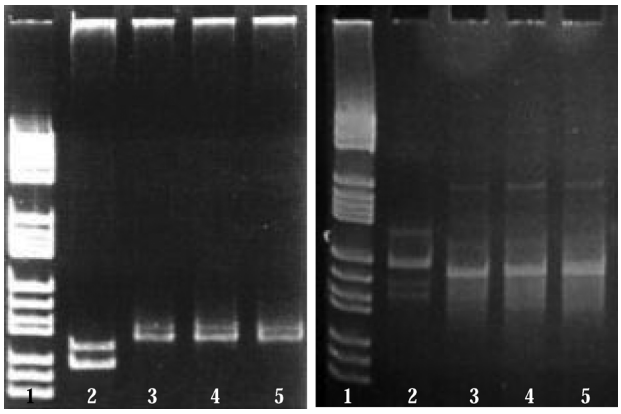

Figure 2. ***(a)*** *PCR-analysis of case 1 shows a distinct band revealing rearranged TCR (dot). Lane 1 = molecular weight standard; lane 2 = positive control (CCL119, cell line); lane 3, 4 and 5 = patient´s tissue. (b) PCR-analysis of case 3 demonstrating rearrangement of the immunoglobulin heavy chain gene (dot). lane 1 = molecular weight; lane 2 = positive control (human tissue with monoclonal B-cell lymphoma); lane 3, 4 and 5 = patient´s tissue.*

but most of the anaplastic tumor cells showed strong positivity for vimentin and CD45RB (leucocyte common antigen) with great variability of staining intensity (*Figure 1c*). Many tumor cells were CD3-, CD8- (*Figure 1d*) and CD43-positive, but negative for all other markers. However, they showed a variable cytoplasmic reactivity with antibodies to immunoglobulin light chains with a slight predominance of kappa light chain.

Gene rearrangement studies of the immunoglobulin heavy chain gene were in germline configuration. A rearrangement of the T-cell receptor gamma chain gene of the anaplastic tumor portion revealed monoclonality, allowing the diagnosis of a peripheral T-cell lymphoma, unspecified (*Figure 2a*).

Case 2

A 71-year-old male patient was admitted to the hospital with dyspnoea, left sided pleural effusion and multiple lung nodules measuring up to 6 cm in diameter, which consisted of a tubular and cribriform moderately differentiated adenocarcinoma with metaplastic ossification, suspicious of metastatic colonic carcinoma. Colonoscopy revealed a circular tumor in the cecum and the patient underwent palliative ileocolectomy. 10 cm proximal to the cecal tumor, a second tumor was found in the ileum and interpreted as a metastasis of the cecal carcinoma.

Microscopically, the colonic tumor was a tubular, moderately differentiated adenocarcinoma infiltrating into the mesocolic fat (*Figure 3a*). Lymphatic invasion was obvious with metastases in 6 of 25 pericolic lymph nodes. The ileal tumor was diagnosed as a NHL with blasts with large nuclei of varying size and shape, prominent nucleoli and numerous mitotic figures (*Figure 3b*). Immunohistochemistry revealed positivity with Abs to CD20 (*Figure 3c*) and to kappa light chain. Some of the tumor cells were EBV-positive. 10% of the tumor cells were bcl-2-positive, about 30% revealed an intranuclear positive immunoreaction with an antibody to bcl-6 (*Figure 3d*). The proliferation fraction as revealed by MIB-1 immunostaining was 80%. The tumor cells showed no reactivity with antibodies to CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD10, CD23, CD30, CD43, CD56, CD57, EMA and pancytokeratin.

Molecular genetic analysis of the NHL was performed in two different laboratories (Institute of Pathology, University of Graz, Austria and Institute of Pathology, Landeskrankenhaus Klagenfurt, Austria), showing no rearrangement of the immunoglobulin heavy chain gene.

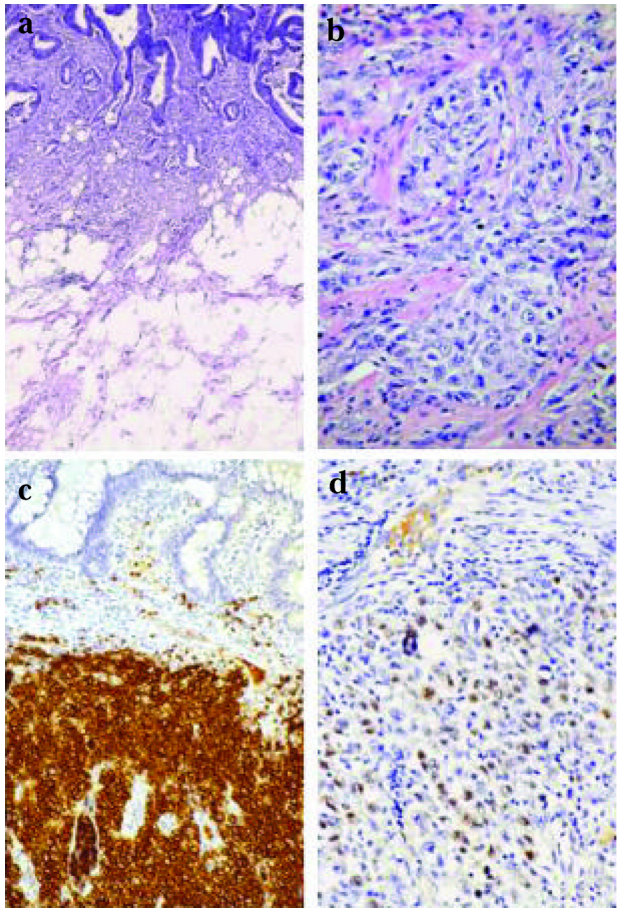

Figure 3. *Case 2. Concomitant B-cell NHL and adenocarcinoma.* ***(a)*** *Moderately differentiated tubular adenocarcinoma infiltrating mesocolic fat.* ***(b)*** *Diffuse large B-cell lymphoma in the ileum with large tumor cells with abundant cytoplasm (H&E).* ***(c)*** *The lymphoma cells strongly react with Abs against CD20.* ***(d)*** *About 30% of the tumor cells show positivity with Abs against bcl-6. (a, 40x; b, 200x; c, 40x; d, 100x).*

Case 3

A 55-year-old woman was admitted to the hospital with diarrhoea. At colonoscopy, a polypoid tumor measuring 1.4 cm in diameter was found in the sigmoid colon and a polyp measuring 3 mm in diameter in the ileum along with enlarged lymph nodes in the ileocecal region. The sigmoid resection specimen contained a moderately differentiated tubular adenocarcinoma. The ileal polyp and the enlarged regional lymph nodes showed infiltration by atypical small lymphocytes with round and oval nuclei with prominent nucleoli in a follicular and diffuse growth pattern (*Figure 4a*). The tumor cells revealed a specific reaction with antibodies against CD10 *(Figure 4b),* CD20, bcl-2 *(Figure 4c),* bcl-6 and lambda light chain. Antibodies against CD21 and CD23 stained an irregular network of follicular dendritic reticulum cells in the follicular areas. There was no reactivity with antibodies against cyclin D1 and CD30. The proliferation fraction (MIB-1 immunostaining) was about 20%. The diagnosis was follicular lymphoma, Grade 2. PCR showed rearrangement of the immunoglobulin heavy chain gene (*Figure 2b*).

Discussion

Only few references on collision tumors of NHL and carcinoma in the large bowel[5] and concomitant tumors of adenocarcinoma in the large bowel and NHL in the small bowel[8] exist. One reason may be under recognition, since differentiation between anaplastic carcinoma and high grade lymphoma cannot be made with certainty on morphological grounds only, especially when the immunohistological profile is equivocal. Cytokeratin-positive individual tumor cells in lymphomas of B-cell lineage,[11] and anaplastic large cell lymphomas[7] have been described. In our case (case1), however, the cytokeratin-positive cells could have been dispersed cells of the adenocarcinoma. Alternatively, cytokeratin positivity could be due to phagocytic uptake of cytokeratin fragments from degenerating carcinoma cells.[7] However, coexpression of cytokeratin in T-cell-lymphoma cannot be ruled out.[11] The cytoplasmic reaction with Abs to light chain in the T-cell-derived tumor cells is suspicious for non-specific uptake of immunoglobulin light chain material, a phenomenon often seen in large lymphoid cells.[17] In this context, the preceding paraproteinemia in patient 2 is suggestive of an immuno-defending mechanism against the adenocarcinoma. Whether malignant transformation of residential lymphoid tissue occurs as a consequence of an exaggerated immunoreaction, e.g. to a carcinoma, remains an unsolved issue.

Molecular genetic analysis is of special importance for the diagnosis of collision tumors consisting of poorly differentiated neoplasms, such as peripheral T-cell lymphoma and anaplastic carcinoma, when immunohistochemistry is inconclusive. We believe that collision tumors consisting of large cell NHL and carcinoma will be detected more often if molecular genetic analysis was used more extensively.

In summary, pathologists should be aware of the existence of collision tumors in the small and large intestines. Appropriate selection of immunohistochemistry may help to establish the diagnosis. Inconclusive results of

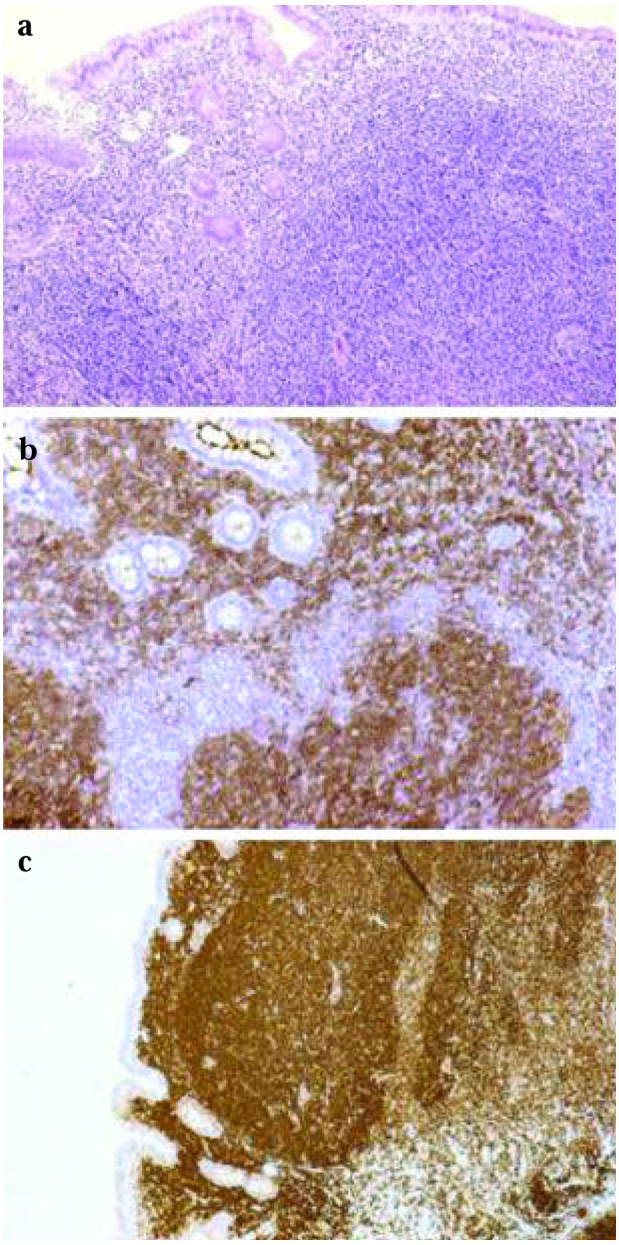

Figure 4. *Case 3. Concomitant follicular center lymphoma and adenocarcinoma.* ***(a)*** *Ileal mucosa and submucosa with follicular infiltrate by atypical mainly small lymphocytes (H&E).* ***(b)*** *The lymphoma cells show a specific immunoreaction with Abs against CD10 and* ***(c)*** *bcl-2. (a, 40x; b, 40x; c, 40x).*

immunohistochemistry can be resolved by molecular analysis, especially when lymphomas are part of the collision tumors.

Acknowledgement

The authors are grateful to Prof. H. Denk for his critical discussions and the final editing of this paper.

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