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Authors

Cooperberg, Matthew R
Fiedler, Paul N

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Ki-1 Anaplastic Large-Cell Lymphoma Occurring at the Site of Ileocolonic Anastomosis in a Patient Treated Surgically for Colonic Adenocarcinoma: Case Report and Review of the Literature

Matthew R. Cooperberg, BA, and Paul N. Fiedler, MD

Systemic anaplastic large-cell lymphoma is an uncommon type of non-Hodgkin lymphoma characterized by strong expression of the Ki-1 (CD30) antigen. Gastrointestinal involvement typically is less common than in other types of non-Hodgkin's lymphoma. We report a case of CD30-positive anaplastic large-cell lymphoma occurring at the site of colonic anastomosis in an elderly patient who had been treated for colonic adenocarcinoma by right hemicolectomy 10 years previously. The lymphoma was a 2-cm mass composed of large, atypical cells infiltrating the mucosa, submucosa, and muscularis propria. Immunoperoxidase stain was strongly positive for Ki-1, and negative for LeuM1, L26, UCHL1, EMA, and cytokeratin. There have been numerous reports of unusual extranodal presentations of systemic anaplastic large-cell lymphoma; the only previously reported case involving the colon, however, occurred in the context of ulcerative colitis. Anastomotic recurrence is a relatively common complication of surgical therapy for adenocarcinoma, but the recurrent tumors are invariably adenocarcinomas. We are aware of no cases of lymphoma of any type occurring at the site of anastomosis after resection for adenocarcinoma.
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Index Words: Lymphoma, large-cell, Ki-1, anastomosis, surgical, lymphoma, non-Hodgkin, gastrointestinal neoplasms

FIRST described in 1985 by Stein et al,[1] Ki-1 anaplastic large cell lymphoma (ALCL) constitutes an uncommon subset of non-Hodgkin lymphoma, characterized by strong expression of the Ki-1 (CD30) antigen. The World Health Organization classification[2] recognizes two forms of ALCL, cutaneous and systemic. The former shares many characteristics of lymphomatoid papulomatosis and regressing atypical histiocytosis, including frequent spontaneous regression. In contrast, systemic ALCL typically presents in advanced stage, with systemic symptoms and an aggressive clinical course.[3,4]

Gastrointestinal involvement is less common in ALCL than in other lymphomas; a number of rare presentations have been described, including primary tumors of the gut. The only known case in the colon, however, occurred in the context of ulcerative colitis. We report a case of CD30-positive ALCL occurring at the site of colonic anastomosis in an elderly patient who had been treated for colonic adenocarcinoma by surgical resection 10 years previously. We are aware of no previously reported case of ALCL of the colon, nor of any lymphoma occurring at the site of surgical anastomosis.

Case Report

The patient, an 89-year-old man with a history of colon cancer, was admitted to the hospital in March 1998 for treatment of benign prostatic hypertrophy by transurethral resection of the prostate. Histologic examination of the prostate chips showed prostatic adenocarcinoma, Gleason score 3/10, involving 10% of the tissue examined (stage T1b). During recovery from this procedure, the patient reported chronic constipation and rectal pain; a surgical consultation was obtained. Examination revealed impacted stool in the rectum and an anal fissure with severe perianal excoriation. The stool was guiac-

From Yale University School of Medicine, New Haven; and the Department of Pathology, Hospital of St Raphael, New Haven, CT.

Address reprint requests to Paul N. Fiedler, MD, 1450 Chapel St, New Haven, CT 06511.

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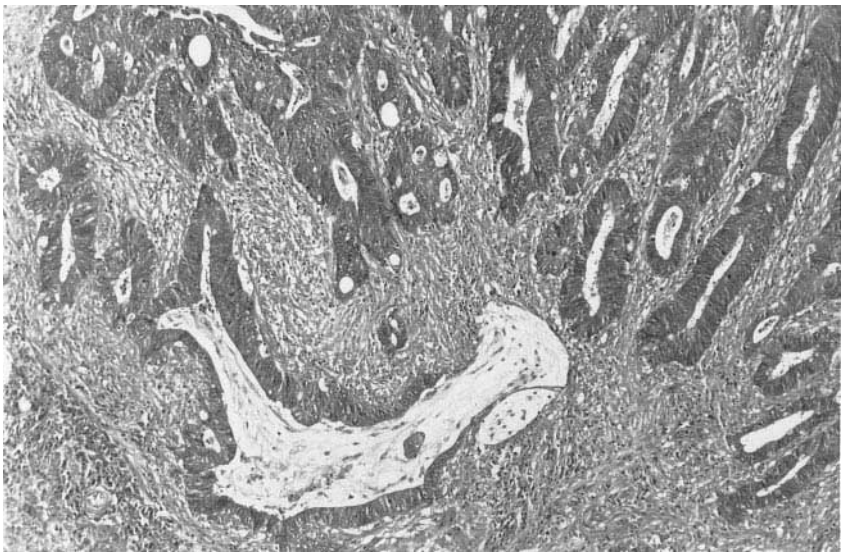

Figure 1. Well-differentiated, mucinous adenocarcinoma of the colon, treated by right hemicolectomy. (Medium power.)

negative. Laboratory evaluation was normal aside from elevated blood urea nitrogen and creatinine secondary to his chronic urinary obstruction. The patient had undergone right hemicolectomy for colon cancer 10 years previously. The resected tumor was a well-differentiated mucinous adenocarcinoma involving the cecum and ileocecal valve, with invasion of the serosal adipose tissue (Fig 1). None of the 33 resected mesenteric lymph nodes were involved by tumor.

A barium enema showed two filling defects at the area of the ileocolonic anastomosis. Subsequent colonoscopy revealed a polypoid mass and a second, friable mass in the area of the prior anastomosis. Multiple biopsies were taken, revealing mucosal infiltration by highly atypical cells with hyperchromatic, large, irregular nuclei, suspicious for malignancy. Based on the results of the biopsy, the anastomotic site and part of the transverse colon were resected.

Pathology

The resected segment of bowel contained a 2-cm submucosal mass in the region of the prior anastomosis, which showed a uniform, tan cut surface. Histologic sections showed large, atypical cells infiltrating the mucosa, submucosa, and muscularis propria. Nucleoli were prominent, mitoses were frequent, and many cells were multinucleated (Figs 2, 3). Immunoperoxidase stain was strongly positive for Ki-1 (Ber H2; Signet, Dedham, MA [CD30]), and displayed a crisp, membranous staining pattern. LeuM1 (Becton Dickinson, San Jose, CA), L26 (Biogenex, San Ramon, CA), UCHL1 (Biogenex), EMA (Biogenex), and cytokeratin (AE1/AE3; Boeringer, Mannheim, Germany) stains were negative. The lesion elicited an inflammatory response predominantly composed of small lymphocytes and occasional eosinophils. An adjacent mesenteric lymph node showed a similar neoplastic infiltrate confined to the sinusoids. There was no evidence of recurrent colonic adenocarcinoma. Gene rearrangement studies for clonal T-cell receptor and immunoglobulin gene rearrangements were negative by polymerase chain reaction. Based on the morphologic and immunophenotypic characteristics, a diagnosis of Ki-1 ALCL was rendered.

Discussion

Anaplastic large-cell lymphoma accounts for 2% to 8% of all non-Hodgkin's lymphomas. Compared to nonanaplastic, diffuse, large-cell lymphoma, ALCL has a higher male to female ratio and affects younger patients[4]; some series report a bimodal distribution, with peaks both in the third and the seventh decades.[5,6] Anaplastic large-cells lymphoma is more likely to present in advanced stage, with present B symptoms and extranodal involvement, particularly of the skin and lung.[4] It typically has a better response to chemotherapy, and a better prognosis than non-ALCL.[4,7]

Rare primary extranodal presentations of systemic ALCL have been noted in bone[8] brain[9] endobronchial tree,[10] chest wall,[11] heart,[12] and masticator space.[13] Other presentations also have been noted in the context of human immunodeficiency virus infection[14] and post-transplant immunosuppression.[15] In up to one third of cases, ALCL is associated with Epstein-Barr virus infection and genomic integration into tumor cell DNA.[16] Hu-

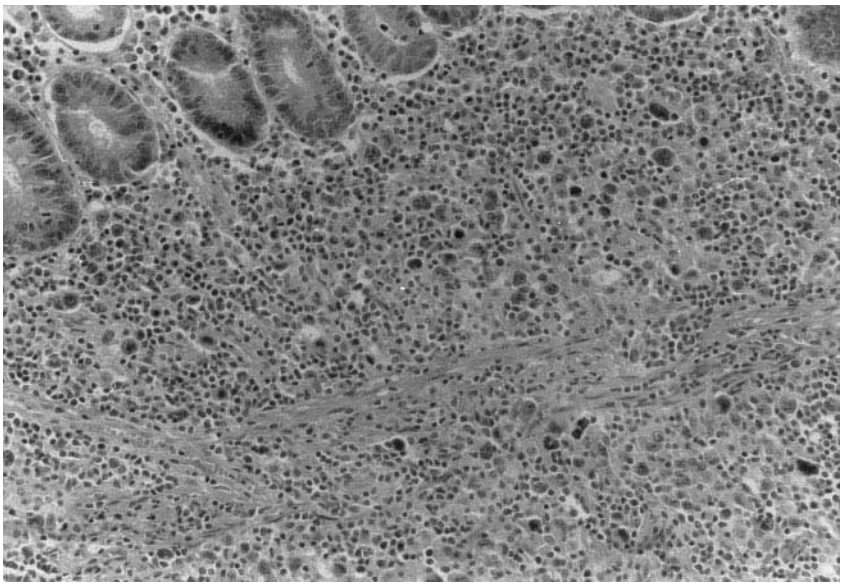

Figure 2. Ki-1 anaplastic large cell lymphoma arising at the ileocolonic anastomosis 10 years postsurgical resection. The tumor cells are present in the mucosa and submucosa. (Medium power)

man T-cell lymphotropic virus-I also has been implicated in ALCL pathogenesis through proviral integration.[17] One case of ALCL arose from donor cells after allogenic bone marrow transplant.[18] Anaplastic large-cell lymphoma also may present with a prominent leukemic phase,[19] or with malignant mesothelial effusions.[20] It has been reported to mimic miliary tuberculosis[21] and noduloulcerative tertiary syphilis,[22] and should be considered in the differential diagnosis of disseminated cancer with an unknown primary tumor.[23]

Gastrointestinal involvement in ALCL typically is less common than in non-ALCL.[24] Tilly et al[4] found 10 of 146 (6.8%) ALCL patients with gut involvement, versus 277 of 1,695 (16.3%) non-ALCL patients ($P < 002$). Specific gastrointestinal sites of involvement reported include the esophagus,[25] pancreas,[26] and stomach,[27] as well as the small and large bowel in the setting of ulcerative colitis.[28]

Ki-1 ALCL may express T- or B-cell antigens; it also may express both or neither.[4] The B-cell variant is recognized in the Kiel classification,[29] but is conflated with other diffuse large B-cell lymphomas under the Revised European American Lymphoma

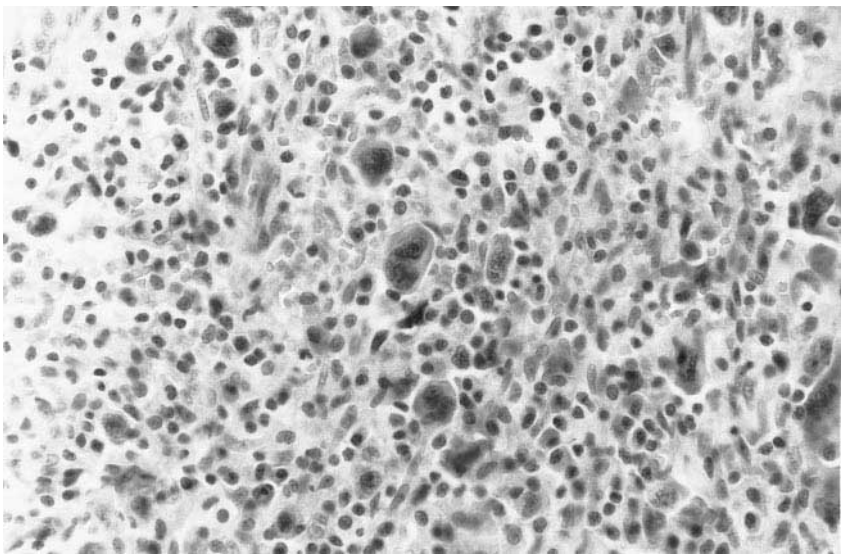

Figure 3. Ki-1 anaplastic large cell lymphoma. (Highpower.)

Classification and World Health Organization schemas.[2] Kadin[6] describes a number of morphologic variants, including common type (pleomorphic cells with abundant cytoplasm, one or multiple nuclei, and huge nucleoli), monomorphic, small cell predominant, lymphohistiocytic, neutrophil rich, Hodgkin's disease like, and sarcomatoid. Anaplastic large-cell lymphoma has variable cytologic morphology that may make it particularly difficult to diagnose. Classically, it features pleomorphic, large neoplastic lymphoid cells, spreading contiguously, particularly in lymph node sinuses. Seventy-five percent to 100% of cells express CD30 in cell membrane and/or Golgi zone stains; 78% also express CD45.[4]

In its histiocytic form, it may simulate carcinoma[30]; its sarcomatoid phenotype may likewise mimic primary soft-tissue sarcoma.[2,3] It also may develop from other lymphomas. McCormick et al[32] report a patient with mucosa-associated lymphoid tissue, monocytoid B cell, and anaplastic large-cell lymphomas, all three with identical gene rearrangements.[32] In another recently reported case, ALCL followed Ewing sarcoma and combination chemotherapy and radiotherapy[33]; it also has been reported in a patient with polycythemia vera.[34]

CD30 is a cell-surface antigen that ALCL shares with Hodgkin's disease (HD).[35] The CD30 ligand is expressed on resting B and activated T lymphocytes, and can induce apoptosis in CD30+ cell lines.[36] Levels of soluble CD30 are also elevated in ALCL,[37] and may explain the B symptoms that patients with the disease experience.[38,39] Furthermore, elevated soluble CD30 is thought to protect against CD30 ligand-mediated cell death, and may correlate with a poor prognosis.[36] Patients with ALCL also may have high serum levels of CA125 and IL-6,[40] and galectin-3.[41]

Schmidt et al[42] suggest that although Hodgkin's disease and ALCL are both CD30+, the BerH2 staining pattern within the cell may help clarify the diagnosis. In their series of 23 HD cases, 74% displayed predominantly cytoplasmic staining; only 17% presented with prominent membrane-bound staining. In contrast, of 13 cases of ALCL, 77% displayed a membranous pattern, as did two cases of ALCL secondary to primary HD, and 40% of tumors they considered to be intermediate between ALCL and HD morphologically.[42] The tumor reported in this case showed crisp membranous staining, thus favoring the diagnosis of ALCL over HD.

Many cases of ALCL are associated with a t(2;5)(p23;q35) translocation, which produces a fusion gene product of the tyrosine kinase anaplastic lymphoma kinase to nucleophosmin.[43] When present, this translocation distinguishes ALCL clinicopathologically from HD, and has been proposed to be intimately involved in the pathogenesis of some cases of ALCL.[44] However, while consistently absent in HD, the t(2;5) translocation is only present in at most 60%,[3,45] and as few as 17%[46] of adult ALCL cases, suggesting that it may be a specific, but not a sensitive indicator of ALCL. More recently, a second translocation has been identified in a small series of cases showing t(1;2)(q25;p23), encoding a fusion between anaplastic lymphoma kinase and the nonmuscular tropomyosin TPM3.[47]

A few earlier studies also reported clonal rearrangements in the T-cell receptor genes in T-cell ALCL and in immunoglobulin genes in B-cell ALCL. Indeed, it was based on such rearrangements that Herbst et al[48] proposed classifying ALCL into T-, B- and null-type tumors. They reported rearrangements in 15 of 22 (68%) of ALCL, compared with 11 of 39 (28%) of HD.[48] However, other studies found rearrangements in as few as two of 19 (11%) of ALCL cases.[1]

The gut is the most common site of all primary extranodal lymphoma,[49] accounting for roughly 5% of non-Hodgkin's lymphomas[50]; gastrointestinal lymphoma is nonetheless a rare tumor, with an incidence of 1.6 per million annually.[51] The peak incidence is in the sixth to eighth decades, with a 2:1 male predominance. The stomach accounts for most of these tumors[27]; only 10% to 20% occur in the colorectum, accounting for 0.2% to 0.65% of colorectal malignancy. The large majority of colorectal lymphomas localize to the ileocecal valve.[50] In some countries, the proportion of gastrointestinal lymphomas involving the colorectum may be higher–up to 45% in India, for example[52]–suggesting an as yet unidentified environmental or genetic etiology. Acquired immunodeficiency syndrome, immunosuppression, and inflammatory bowel disease are known predisposing conditions.[49] The large majority of colorectal lymphomas are B-cell tumors, with aggressive, large-cell features.[53] Primary ALCL of the colorectum has been reported only once before, in the context of ulcerative colitis.[28]

Between 5% and 18% of colonic adenocarcinoma resections are complicated by anastomotic recurrence. These constitute a significant fraction of the 10% to 25% of carcinomas that recur locally, usually within 2 years of surgery. Such recurrences are presumed to be caused either by tumor cell implantation at the time of surgery, or by metachronous carcinogenesis; in either case the suture line is thought to be more vulnerable because of the trauma of surgery, with subsequent inflammation and hyperplasia.[54] These recurrent tumors are invariably adenocarcinomas. We are aware of no case of lymphoma occurring at the site of anastomosis.

In summary, we present a case of large-cell lymphoma, with a Ki-1-positive staining pattern characteristic of ALCL, presenting at the site of anastomosis after ileocolonic resection for adenocarcinoma of the colon. This is the first reported case of colonic Ki-1 lymphoma not associated with ulcerative colitis, and the first case of a malignancy other than adenocarcinoma occurring at the anastomotic site.

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