

ANAPLASTIC KI-1 (CD30) POSITIVE LARGE CELL LYMPHOMA OF THE STOMACH MIMICKING HODGKIN'S DISEASE: A CASE REPORT AND REVIEW OF THE LITERATURE

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The stomach is considered the most common site of primary gastrointestinal lymphoma.¹ The majority of these cases are classified as non-Hodgkin's lymphoma (NHL),¹ and with the recent adoption of the concept of mucosa-associated lymphoid tissue (MALT),^{2,3} they are now classified as low- and high-grade MALT-lymphomas.⁴ Primary Hodgkin's disease of the gastrointestinal tract is rare.^{1,5,6-8} However, the stomach remains the most common site of primary extranodal gastrointestinal Hodgkin's disease.^{6,9-11} The previously quoted figure of 9% as the proportion of Hodgkin's disease relative to NHL involving the stomach⁹ is controversial and too high. This is certainly due to inclusion of such pleomorphic, anaplastic lymphomas as Hodgkin's disease when a full panel of immunohistochemistry is not performed. Of all NHL, the one that usually mimics carcinoma or Hodgkin's disease is the anaplastic CD30 (Ki-1) positive large cell lymphoma (ALCL),¹²⁻¹⁸ which was included in the updated Kiel¹⁹ and the REAL classifications of lymphoid neoplasms.²⁰ The case presented here illustrates such morphology misdiagnosed as Hodgkin's disease.

Materials and Methods

A 43-year-old Syrian male was admitted with a history of upper abdominal pain and recurrent nausea and vomiting for the previous eight months. The pain was localized in the epigastrium, dull in character and was aggravated by eating. There was no history of hematemesis. He was having repeated episodes of melena and had lost 16 kg body weight over the last four months. Past, family, social and personal history was not remarkable.

Physical examination revealed a young male with signs of emaciation. He was pale but not jaundiced or cyanosed, and his vital signs were normal. Peripheral lymph nodes

were not palpable. Examination of the abdomen showed an ill-defined mass in the epigastrium, 10x8 cm in size, non-tender with irregular surface, and firm in consistency. Liver and spleen were not palpable and there was no ascites.

Laboratory investigations showed CBC hematocrit 0.27, WBC $5.8 \times 10^9/L$, hemoglobin 90 g/L, and peripheral blood smear and absolute indices suggestive of microcytic hypochromic anemia. Total serum protein was 54 g/L, with serum albumin of 27 g/L. Liver enzymes and other relevant serum chemistry tests were normal.

Upper GI endoscopy showed a fungating mass at the pre-pyloric area, with extension to mucosal folds and narrowing of the lumen of the stomach. Multiple biopsies were taken for histopathological examination. These revealed an anaplastic malignant neoplasm consistent with poorly differentiated adenocarcinoma. No immunohistochemistry was performed. CT scan of the abdomen revealed thickened gastric pylorus with polypoidal projections from its wall (Figure 1). A small oval soft tissue mass was seen just underneath the anterior abdominal wall close to the region of pylorus. Pancreas, spleen, liver, kidneys and adrenals were normal and there was no para-aortic lymphadenopathy.

Upon the diagnosis of gastric malignancy, the patient was posted for surgery. The intraoperative findings were a large gastric tumor in the antrum infiltrating up to the serosa of the stomach, with an enlarged lymph node at the greater curvature just proximal to the pylorus, and a prominent pancreaticoduodenal lymph node. The liver was normal and there was no ascites. Partial gastrectomy with end-to-side retrocolic gastrojejunostomy was done. Pancreatoduodenal lymph node was excised. The specimen was fixed in 10% buffered formaldehyde. Paraffin sections were prepared and examined using routine hematoxylin and eosin (H&E) stain.

In 1998, immunohistochemistry was performed on sections retrieved from formalin-fixed paraffin blocks using an avidin-biotin-peroxidase complex method,²¹ utilizing the microwave for antigen retrieval. A panel of monoclonal antibodies against Ber-H2/CD30 (Dako), Leu MI/CD15 (Becton Dickinson), LCA/CD45 (Dako), UCHL-1/CD45RO (Dako), L26/CD20 (Dako), KP1/CD68 (Dako),

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Accepted for publication 12 April 1999. Received 16 December 1998.

E29/EMA (Dako), CD3 (Dako), Vimentin (Dako), and AE1-AE3 Cytokeratin (Boehringer Mannheim) was performed.

Results

Gross examination of the partially resected 12x7x4 cm stomach revealed an exophytic 5x4 cm gastric tumor, which was infiltrating up to the serosa and had a fish-flesh gray-white cut surface. The resection margins were free of the tumor. Several perigastric lymph nodes submitted also showed fish-flesh homogenous appearance.

In 1994, based on the anaplastic morphology of the gastric neoplasm, the presence of Reed-Sternberg-like (R-S-like) cells and a negative cytokeratin on immunohistochemistry, a diagnosis of Hodgkin's disease of the stomach was given. Based on this diagnosis, therapy was started.

Review of the case in 1998 in a retrospective study of gastric malignancies revealed a gastric tumor with surface ulceration of a mucosal neoplasm that extended deep into the wall and serosa. The tumor was formed of sheets of pleomorphic cells, with small and large embryo-like multilobated nuclei having prominent nucleoli and abundant cytoplasm (Figure 2). A variable proportion of small lymphocytic cells were seen, but eosinophils and neutrophils were very scanty. A few binucleate R-S-like cells were seen (Figure 3), in addition to rare cells with bizarre wreath-like multilobated nuclei. A transition between the relatively small-size tumor cells and the larger multinucleated cells was always observed. The lymph nodes showed the same histology with a sinus, carcinoma-like pattern of involvement being very apparent (Figure 4).

The majority of the neoplastic cells, including the giant R-S-like forms, reacted positively for CD30 in a membrane- and dot-like pattern and negatively for CD15 antibodies (Figure 5). They were also positive for CD45, vimentin and focally positive for EMA. Reaction for T-cell CD45RO and CD3 was negative, while a few tumor cells reacted positively for B-cells CD20 antibodies. The pancytokeratin marker AE1-AE3 was negative in the tumor cells. The pleomorphic morphology of this lymphoid neoplasm, the sheet-like and sinus pattern of involvement of lymph nodes, combined with the immunohistochemical reaction of the tumor cells, reclassifies this neoplasm as primary gastric CD30 (Ki-1)-positive ALCL stage II (IE), due to perigastric lymph node involvement. In situ hybridization for EBV mRNA was not performed.

The postoperative course was uneventful. Subsequent bone marrow aspiration did not show evidence of lymphomatous infiltration. Chemotherapy was started and the patient received 6 cycles of COPP and ABVD monthly on an alternate basis over six months. Upper gastrointestinal endoscopy done eight months after surgery was normal. Biopsies obtained through endoscopy showed focal collections of plasma cells and eosinophils with areas

of intestinal metaplasia, but no evidence of recurrent or residual malignancy. Repeat CT scan of the abdomen shortly after the endoscopy showed normal stomach. There was no evidence of para-aortic lymph node enlargement. At the latest follow-up in February 1998, almost four years after the diagnosis, the patient was alive and well with no evidence of residual tumor, clinically or at endoscopy.

Discussion

Presentation of Hodgkin's disease (HD) as a localized extranodal process unassociated with lymphatic tissue involvement is quite rare, occurring in less than 1% of patients with HD.⁵ In the NCI study,⁶ only six patients with a histologically reconfirmed diagnosis of HD were identified during the period 1953-1990. Of all six cases, however, four involved the stomach. Such a rare diagnosis should, therefore, be confirmed by combined classic histopathologic and immunophenotypic features.^{7,8,10,11} This is supported by the fact that in several retrospective studies the cases that were originally diagnosed as HD were all re-classified as NHL of a large cell type after re-examination.^{9,22} Therefore, the predominant gastric lymphoid malignancy is NHL,^{1,4} which has increased in frequency, in contrast to gastric carcinoma, which has shown a decline in both incidence and mortality rates over the past few decades.^{23,24} These lymphomas were originally classified according to criteria developed for nodal lymphomas.^{25,26} However, with the recent adoption of the concept of MALT,^{2,3} most of these lymphomas have been classified as low- and high-grade MALT-lymphomas,⁴ characterized by the presence of lymphoepithelial lesions (LEL). Only 12 of the 60 cases reported by Hsi et al.⁴ lacked LEL and were thus classified as diffuse large cell lymphomas (DLCL). Some of these gastric DLCL may assume a pleomorphic anaplastic morphology, with sheet-like growth pattern that may simulate carcinoma¹² and

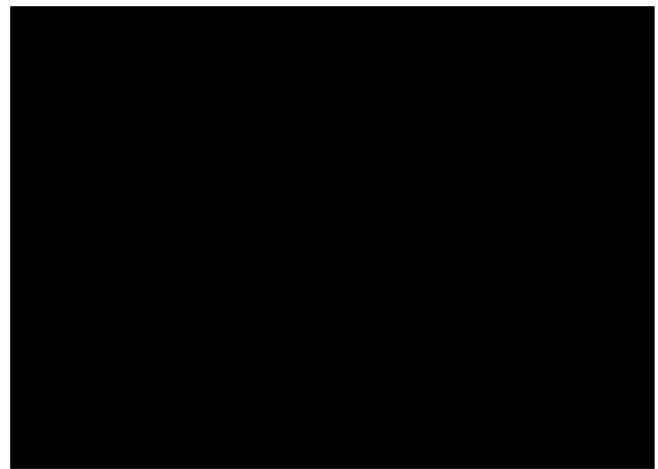


FIGURE 1. CT scan of the abdomen, showing thickened gastric pyloric region with polypoidal projections from its wall.



FIGURE 2. Sheet of anaplastic cells with pleomorphic nuclei having prominent nucleoli in the stomach mucosa (H&E, 125x).



FIGURE 3. Scattered cells with embryo-like nuclei having prominent nucleoli and multinucleated R-S-like cells with prominent eosinophilic nucleoli (H&E, 275x).

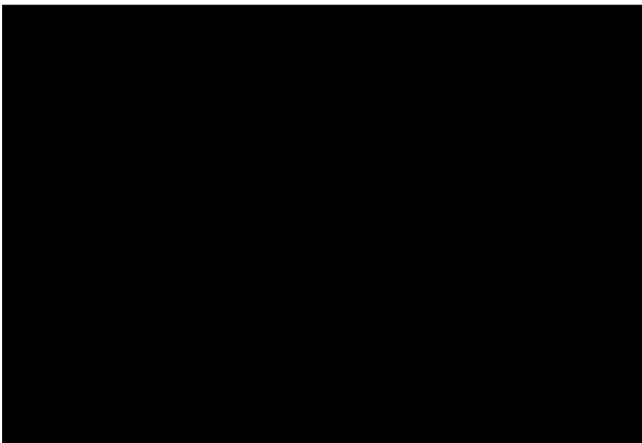


FIGURE 4. Sinus and paracortical involvement of lymph node with sheet-like pattern of growth of neoplastic cells (carcinoma-like) (H&E, 125x).

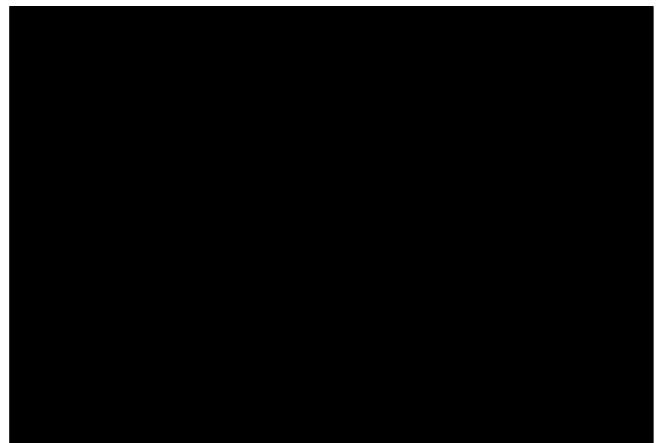


FIGURE 5. Membrane and dot-like pattern of immunostaining in tumor cells, including the R-S-like cells. Immunohistochemistry for Ber H2/CD30x275.

may also contain cells with large multilobated nuclei, R-S-like, that may give rise to a false diagnosis of HD.¹⁷ Some of the large cell lymphomas with such morphology are characterized by being CD30-positive and are recognized mostly at nodal sites,^{15,17,18} but also at extranodal sites.^{12,13,16} In the study of Hsi et al.,⁴ however, immunohistochemistry for CD30 was not included among the panel of antibodies used. These lymphomas are now included in the updated Kiel classification,¹⁹ as well as the REAL classification of lymphoid neoplasms.²⁰ Primary CD30-positive ALCL of stomach are very rare.^{12,13,27,28} In our patient, a diagnosis of ALCL CD30+ was made, where the tumor cells were arranged in sheets, having abundant faintly eosinophilic cytoplasm and large nuclei with prominent eosinophilic nucleoli. A variable proportion of large, bizarre, often multinucleated, cells in a background of small lymphocytes raised the possibility of HD. However, these cells reacted positively for Ber H2/CD30 and negatively with antibodies to Leu MI/CD15.

Furthermore, co-expression in our case of LCA/CD45 and EMA practically ruled out HD.^{13,29,30} However, in situ hybridization for EBV mRNA was not performed to further support this contention. Vimentin was positive in all tumor cells, as noted previously.^{13,17,31} The sinus pattern of involvement in lymph nodes raises the possibility of carcinoma excluded by the negative cytokeratin reaction.³¹ Most of the CD30-positive ALCL were of T-cell or null cell lineage.^{12,15,18} However, our case showed tumor cells positive for B cell L26/CD20, similar to the report of Paulli et al.,¹³ where three cases out of six were of B-cell lineage. It must, however, be pointed out that CD30 defines a lymphocyte activation antigen and is expressed by R-S cells and some non-lymphoid neoplasms.^{14,32}

The stomach is the most common site of primary extranodal lymphomas in adults.²⁴ Our case conforms with criteria set for the diagnosis of primary gastric lymphomas, defined as malignant lymphomas, in which the presenting signs/symptoms are referable to the gastrointestinal tract,

with the major tumor burden located in the stomach.⁴ In a previous publication, Dawson et al.³³ proposed a set of criteria for the diagnosis of primary gastrointestinal lymphomas, including: 1) absence of peripheral lymphadenopathy at the time of presentation; 2) lack of enlarged mediastinal lymph nodes on chest x-ray; 3) a normal total WBC and differential; 4) predominance of the bowel lesion at the time of laparotomy with the only lymph nodes obviously affected being those in its immediate neighborhood; and 5) the liver and spleen not showing any lymphomatous involvement. Our present case fulfills all these criteria.

The prognosis of patients with CD30+ ALCL is reported to be poor, with an overall median survival of 13 months,¹⁵ except for the primary cutaneous form, which has a favorable prognosis, with an overall median survival of 42 months. These figures might raise doubt about the diagnosis in our patient, who was free of disease for almost four years post-treatment. However, the age (≤ 40 years) and the stage (I & II) have been quoted as being associated with long survival.¹⁵ Furthermore, in primary gastric lymphomas, the clinical stage has been found to be the only significant factor in relapse-free and disease-specific survival.⁴ Similarly, in the study of Paulli et al.,¹³ three of six cases of primary gastric C30+ ALCL achieved complete remission with no evidence of disease 12-18 months on last follow-up. Our case was similar in stage—stage II (1E)—achieving longer survival. Comparatively, five of eight cases reported by McCluggage et al. were alive in remission between 1 and 8 years following chemotherapy.¹⁷ Incidentally, five of these cases had originally been diagnosed as HD due to extensive eosinophilic or neutrophilic infiltration.¹⁷ Nakamura et al., in a report of a large series of gastric lymphomas, found that B-cell phenotype, stage and a superficial spreading gross appearance were independent prognostic factors.³⁴ Recently, Nakamura et al.¹⁸ used anti-p80 antibody immunohistochemistry and showed that the detection of p80 is of crucial importance in delineating the biologically distinct entity of primary classical ALCL from HD and HD-like ALCL. The fusion protein p80^{NPM/ALK} is the result of a non-random chromosomal translocation t(2;5)(p23;q35), which is frequently associated with ALCL.³⁵

In conclusion, we report a case of primary gastric Ki-1 (CD30)-positive ALCL with long-term survival following surgery and chemotherapy. Due to the pleomorphic nature of the tumor, the case was initially misdiagnosed as carcinoma on biopsy, and thereafter, as HD on resection specimen. The use of a panel of antibodies, including CD30, CD15, EMA, cytokeratin, vimentin, CD45, CD45RO, CD3 and CD20, is essential to exclude such diagnoses. Future utilization of p80 antibody may prove invaluable in excluding such diagnoses and in particular, HD and HD-like ALCL. It appears that the prognosis of such tumors occurring in the stomach is not as bad as was

previously thought, and furthermore, aggressive chemotherapy may achieve long-term remission.

Acknowledgements

Our gratitude goes to Ms. Khalda Al-Johi for technical assistance and to Mr. Ramesh Kumar for typing the manuscript.

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