Figure 3 Electron micrograph showing signet-ring cells containing large vacuoles.

neutral and acid mucopolysaccharides but stained positively with PSA and PSAP. These cases contrast with Giltman's case,¹ where the signet-ring cells stained positively with periodic acid Schiff with and without diastase digestion. Electromicroscopically, our findings showed that the signet-ring cell appearance was due to an intracytoplasmic vacuole of uncertain origin. Smaller intracytoplasmic vacuoles have been described in prostatic adenocarcinoma.⁸

Tannenbaum showed collections of empty, membrane-lined vacuoles in prostatic carcinoma cells in patients treated with diethylstilbestrol,⁹ which were not present in biopsy specimens before treatment. Our patient was

indeed treated with diethylstilbestrol, but the other reported patients with signet-ring cell prostatic carcinoma were not.^{1,2}

As stated above, the stomach is rarely the site of metastatic tumour.³ Diffuse infiltration of the gastric wall by metastatic tumour, giving a linitis plastica appearance, can be due to metastatic lobular carcinoma of breast.⁴ In two of the 31 cases reported by Cormier,⁴ the infiltrating lobular carcinoma of the breast contained signet-ring cells, but the histology of the gastric metastases was not detailed. In our case the diagnosis of metastatic prostatic carcinoma in the stomach rather than primary gastric carcinoma in a patient with prostatic carcinoma was made possible because of specific prostatic immunohistochemical staining. Discrimination between these two possibilities is important in terms of therapeutic implications. We agree with the previously suggested conclusion^{1,2} that any metastatic signet-ring cell carcinoma of unknown origin in a male can be of prostatic origin and requires immunohistochemical study using PSA and PSAP to confirm or preclude this possibility.

- 1 Giltman LI. Signet ring adenocarcinoma of the prostate. *J Urol* 1981;126:134-5.
- 2 Ro JY, Naggar A, Ayala AG, et al. Signet ring cell carcinoma of prostate. Electron microscopic and immunohistochemical studies of 8 cases. *Am J Surg Pathol* 1988;12:453-60.
- 3 Ming SC. Tumors of the esophagus and stomach. *Atlas of tumor pathology (2nd Series Fascicle 7)*. Washington, DC: Armed Forces Institute of Pathology 1973:253-5.
- 4 Cormier WJ, Gaffey TA, Welch JM, et al. Linitis plastica caused by metastatic lobular carcinoma of the breast. *Mayo Clinic Proc* 1980;55:747-53.
- 5 Epstein JI, Lieberman PH. Mucinous adenocarcinoma of the prostate gland. *Am J Surg Pathol* 1985;9:299-308.
- 6 Cricco RP, Kassis J. Mucinous adenocarcinoma of prostate. *Urology* 1979;14:276-8.
- 7 Odom PG, Donatucci CF, Deshon GE. Mucinous adenocarcinoma of prostate. *Hum Pathol* 1986;17:863-5.
- 8 Ghadially FN. *Diagnostic electron microscopy of tumors*. 2nd edn. London: Butterworths, 1985:363.
- 9 Tannenbaum M. Mucin-secreting carcinoma of prostate. *Urology* 1975;5:543-4.

J Clin Pathol 1992;45:454-456

c-erbB-2 oncogene product expression and prognosis in gastric carcinoma

D A Hilton, K P West

Department of
Histopathology,
Leicester Royal
Infirmary,
Leicester LE1 5WW
D A Hilton
K P West

Correspondence to:
Dr D A Hilton

Accepted for publication
19 September 1991

Abstract

The prognostic value of *c-erbB-2* protein expression was assessed retrospectively in 87 "curative" gastrectomy specimens from patients with gastric carcinoma. Tumours were stained immunohistochemically with the specific antibody 21N. Eight (9%) cases had strong

membrane staining, all of which were of the intestinal type, and lymph node metastases, which showed concordance of staining in seven cases. In contrast to studies in breast cancer, positive cases showed a trend towards better five year survival, but this did not reach significance.

c-erbB-2 (also called NEU and HER-2) is a proto-oncogene that codes for a protein product which shows considerable homology with the epidermal growth factor receptor (EGFR).¹ Several studies have reported amplification of the *c-erbB-2* gene in human neoplasms, particularly in adenocarcinomas.² In carcinoma of the breast *c-erbB-2* amplification correlates well with immunohistochemical staining for the protein product³ and prognostic value.⁴ *c-erbB-2* protein expression has been shown in some gastric carcinomas,⁵ but reports of its prognostic value are conflictual.^{6,7}

Methods

Gastrectomy specimens from 87 patients with gastric carcinoma were retrieved from the files of the Histopathology Department, Leicester Royal Infirmary. All case records were examined and only potentially curative resections (defined as those cases in which macroscopic clearance of tumour was thought to have been achieved and without microscopic disease in the resection margins) were included in this study. Follow up data until death or survival at five years were available.

Tissues were fixed in 10% formol-saline and embedded in paraffin wax. Blocks of the main tumour and lymph node metastases were stained with the polyclonal antibody 21N, specific for the 185 kilodalton *c-erbB-2* protein,⁸ kindly donated by Dr W Gullick.

Dewaxed sections were incubated with 21N, diluted in TRIS-buffered saline (pH7.4) to a concentration of 4 g/ml, for 90 minutes. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide and sections were preincubated with normal swine serum at a 1 in 5 dilution to reduce background staining. A standard avidin-biotin-peroxidase visualisation method was used. Negative control slides were prepared by omitting the primary antiserum and by preincubating the antiserum with the immunising peptide. A known positive case of breast carcinoma was used as a positive control. Tumours showing

membrane staining were regarded as positive and those without as negative.

The tumours were categorised according to the Lauren classification and other tumour variables, including lymph node metastases, were recorded. Statistical analysis of the results was performed using the Kaplan Meier life table analysis and log rank tests.

Results

Strong membrane staining for *c-erbB-2* protein was seen in eight (9%) tumours. In five the staining was focal with positive staining of 10–25% of the tumour cells; in the remainder most tumour cells (50–85%) showed membrane staining. All positive cases had lymph node metastases ($p < 0.01$), which also showed membrane staining in seven of eight cases. Positive cases were all of the intestinal type and the staining was seen in better differentiated areas.

In many cases, including those with membrane staining, there was positive staining of the cytoplasm, sometimes in a supranuclear position, but this was not regarded as significant, as previous work³ has only shown correlation of oncogene amplification with membrane staining.

Tumours with membrane staining for *c-erbB-2* protein had higher mean and median survival at five years, despite the fact that they all had lymph node metastases (table 1). On statistical analysis this difference in survival failed to reach significance at the $p < 0.05$ level, even when only lymph node positive cases were compared (table 2).

Discussion

In this study 9% (eight of 87) of tumours showed membrane staining for *c-erbB-2* protein. This figure is similar to that found in most previous studies,^{6,9} but lower than that found by Falck and Gullick.⁵ However, if their cases showing weak staining are disregarded then the results are similar. Interestingly, our figure of 9% for positive cases is close to the proportion of gastric cancers shown to have amplification of the *c-erbB-2* proto-oncogene.^{2,9,10}

Despite being associated with lymph node metastases membrane staining for *c-erbB-2* protein was associated with a trend to a better prognosis, which would support the findings of a previous United Kingdom study⁶ but contrasts with a more recent report from Japan.⁷ This latter study also found *c-erbB-2* protein expression in poorly differentiated tumours which contrasts with our findings and previous work^{6,9} where expression was confined to well differentiated tumours. The association with an adverse prognosis was not seen in patients with early gastric cancer⁷ but only in advanced gastric carcinomas. Unlike early cases, all advanced cases were given chemotherapy, suggesting that *c-erbB-2* expression may be associated with a poor response to chemotherapy.

Table 1 Results of *c-erbB-2* protein staining

	Number (%)	Mean survival (weeks)	Median survival (weeks)
Positive	8 (9)	110.8	94.5
Negative	79 (91)	87.9	52
Histological type:			
Intestinal	68 (78)	91.4	49.5
Diffuse	13 (15)	80.3	57
Unclassified	6 (7)	45.8	52
Lymph node deposits:			
Present	54 (62)	77.2	49
Absent	33 (38)	103.3	63

Table 2 Survival in lymph node positive cases

<i>c-erbB-2</i> protein staining	% (number) alive at 5 years	Mean survival (weeks)	Median (weeks)
Positive	25 (2)	110.8	94.5
Negative	8.7 (4)	69.8	29

The finding of an improved prognosis in gastric cancers expressing *c-erbB-2* protein is also in contrast to most studies in breast cancer⁴ where expression has been associated with a shorter relapse time and survival. The functional role of *c-erbB-2* protein in gastric carcinoma is unknown and overexpression only occurs in a proportion of tumours. It may be related to a specific mechanism of transformation occurring in better differentiated carcinomas, although further studies are needed to clarify this.

- 1 Yamamoto T, Ikawa S, Akiyama T, *et al.* An erb-B-related gene, *c-erbB-2*, encodes a possible receptor protein similar to the epidermoid growth factor receptor. *Nature* 1986; 319:230-4.
- 2 Tal M, Wetzler M, Josefborg Z, *et al.* Sporadic amplification of the Her 2/neu proto-oncogene in adenocarcinomas of various tissues. *Cancer Res* 1988;48:1517-20.

- 3 Walker RA, Senior PV, Jones JL, Critchley DR, Varley JM. An immunohistochemical and in situ hybridisation study of *c-myc* and *c-erbB-2* expression in primary human breast carcinomas. *J Pathol* 1989;158:97-105.
- 4 Wright C, Angus B, Nicholson S, *et al.* Expression of *c-erbB-2* oncoprotein: a prognostic indicator in breast cancer. *Cancer Res* 1989;49:2087-90.
- 5 Falck VG, Gullick WJ. *c-erb-2* oncogene product staining in gastric adenocarcinoma. An immunohistochemical study. *J Pathol* 1989;159:107-11.
- 6 Jain S, Filipe IM, Gullick WJ, Lineham J. Does *c-erbB-2* expression have prognostic significance in gastric carcinoma? *J Pathol* 1990;161:343A.
- 7 Yonemura Y, Ninomiya I, Yamaguchi A, *et al.* Evaluation of immunoreactivity for *erbB-2* protein as a marker of poor short term prognosis in gastric cancer. *Cancer Res* 1991;51:1034-8.
- 8 Gullick WJ, Berger MS, Bennett PLP, Rothbard JB, Waterfield MD. Expression of *c-erbB-2* protein in normal and transformed cells. *Int J Cancer* 1987;40:246-54.
- 9 Park JB, Rhim JS, Park SC, Kimm SW, Kraus MH. Amplification, overexpression, and rearrangement of the *erbB-2* proto oncogene in primary human stomach carcinomas. *Cancer Res* 1989;49:6605-9.
- 10 Yokota J, Yamamoto T, Miyajima N, *et al.* Genetic alterations of the *c-erbB-2* oncogene occur frequently in tubular adenocarcinoma of the stomach and are often accompanied by amplification of the *v-erbA* homologue. *Oncogene* 1988;2:283-7.

J Clin Pathol 1992;45:456-458

Histological audit of acute appendicitis

M E Herd, P A Cross, S Dutt

Abstract

One hundred retrospective appendectomy specimens were examined in an attempt to study the degree of uniformity and clarity of reporting of this common surgical specimen. There was full agreement in 73 cases and some degree of discrepancy in 27 cases. It is suggested that greater clarity in reporting can be achieved with five reporting categories: (i) established acute inflammation; (ii) no evidence of acute inflammation ("normal"); (iii) features suggestive of early inflammation; (iv) peri-appendicitis; (v) other features, such as granulomata, *Enterobius vermicularis*, tumours, etc.

Some 70 000 appendectomies are performed each year in England and Wales¹ for a clinical diagnosis of acute appendicitis. This makes the appendix one of the more commonly received specimens in a histology department. This ensures that histopathologists should see a regular number of these specimens a year, but does not guarantee that they agree on what they see, or on interpretation. With the current emphasis on medical audit,^{2,3} we felt that the routine reporting of these appendix specimens required a new look with two main aims: (i) can histopathologists report appendix specimens consistently? and (ii) if not, why not?

Methods

The surgical pathology files of our department were searched and 100 retrospective consecutive appendix histology slides and their reports were withdrawn. All the specimens were from the period January to September 1990. The initial slides had been reported by six different histologists during the study period, all post-MRCPath. The slides were reviewed blind by three consultant histopathologists with no macroscopic or clinical details. The issued reports and those of the reviewing pathologists were then compared and any differences noted.

Results

Of the 100 study appendices, 90 were removed for a clinical diagnosis of acute appendicitis, four for persistent right iliac fossa pain, and six as part of another procedure. The average number of pieces of tissue taken from each appendix was four (including the tip and proximal resection margin), with a range of two to 13. Of the 100 appendix specimens reviewed, there was complete agreement between the three reviewing pathologists and that of the initial issued report in 73 cases, with the agreed diagnoses being established acute inflammation in 56 cases; no evidence of acute inflammation in 13 cases; early inflammation in two cases; peri-appendicitis in two cases, and with one case also containing *Enterobius vermicularis*. In 27 cases

Department of
Histopathology, Bury
General Hospital,
Walmersley Road,
Bury, Lancashire
BL9 6PG
M E Herd
P A Cross
S Dutt

Correspondence to:
Dr P Cross

Accepted for publication
18 September 1991