Intraepithelial stage of signet-ring cell carcinoma of the stomach

Histological observations on minute gastric carcinomas have indicated that "differentiated" (intestinal) type carcinomas seem to originate in metaplastic intestinal epithelium and that "undifferentiated" (diffuse) type carcinomas containing signet-ring cells (SRC) seem to originate in non-metaplastic gastric mucosa.1 Dysplastic and in situ changes in intestinal metaplasia associated with differentiated (intestinal) type carcinoma are well known. It is generally believed that SRC gastric carcinoma arises de novo at the glandular neck level2 and forms a layered structure in the lamina propria.3

According to a multistep theory of neoplasia, it is equally possible to have a sequential evolution of the SRC gastric carcinoma from an intermediate intra-epithelial stage. On the other hand, it has already been documented that acid mucin often spread through tissue strictly adhering to pre-existing basement membrane.4 Recently, Ghan-dur-Mnaymneh et al defined the criteria for dysplasia of non-metaplastic gastric epithelium and proposed that it may have a possible association with diffuse type gastric carcinoma.5 The main feature of this dysplasia is the replacement of the differentiated cells lining the glands by undifferentiated cells with a varying degree of atypia, but in the absence of architectural glandular derangement.

We document an additional case of intraepithelial carcinoma associated with multifocal, minute, poorly differentiated adenocarcinoma with an SRC component, in a rested stomach specimen of a 60 year old man. The intraepithelial carcinoma cells ended abruptly at the junction with the adjacent periodic acid Schiff positive foveolar cells (figure). Fusion or severe distortion, or both, of the neighbouring tubules were not detected.

The component cells of the intraepithelial carcinoma were uniformly of a columnar shape with a thin brush border (figure). They showed enlarged, ovoid, vesicular, moderately pseudostratified nuclei with prominent nucleoli (figure). The cytoplasm was generally not stained with periodic acid Schiff, alcin blue, or high iron diamine. Very occasionally these intraepithelial carcinoma cells exhibited small vacuoles, which appeared "optically empty" or contained a variable amount of neutral mucus, sialomucins, and sulphomucins. Atypical mitoses were frequently found. A histological continuity between intraepithelial carcinoma and poorly differentiated adenocarcinoma glands was observed in some areas (figure). Both the poorly differentiated adenocarcinoma cells and isolated SRC showed a granular positivity for sialomucins as well as large cytoplasmic vacuoles, which appeared "optically empty" (figure).

In our case the presence of intraepithelial carcinoma may reflect the proliferative activity of a distinct population of atypical cells which are not fully transformed into malignant cells, being between adenoma and invasive cancer in nature. In fact, besides possessing the ability to migrate along the foveolar wall, the intraepithelial carcinoma cells frequently show morphohistochemical features such as their columnar shape, brush border, and rare mucin granules. By contrast, invasive adenocarcinoma is represented in our case by tumour cells which are capable of forming gland-like structures (poorly differentiated adenocarcinoma) or which show a complete loss of the gland-forming ability (isolated SRC). Moreover, abundant mucous production seems to be a feature seen predominantly in invasive adenocarcinoma and only in a few cells of the intraepithelial carcinoma.

In conclusion, our data indicate the possibility of an intraepithelial stage with peculiar morphohistochemical features during the progression of SRC gastric carcinoma.


In a biopsy sample and in the narrow and peripheral blood.

Chromosome analysis of phytohaemagglutinin stimulated peripheral blood lymphocytes was carried out as mitoses were not observed in unstimulated cultures. Of 48 banded cells, one showed a 46,XX, normal male karyotype and 14 cells showed a complex karyotype of 43,Y, t(5;14)(q26; q11), -12, -13, -20, t(5;7;9)(p22; q11; q12), t(11;19)(q13;p13), del(6)(q13), +1, +mar 2, +mar 3. The translocations t(3;7;9) and t(11;19) appeared to be not completely reciprocal as the derivative chromosome 7 (der7) and der (11) were missing, or involved in the formation of the marker chromosomes. Marker 1 involved the q arm of the deleted chromosome 6 and marker 2 involved der (9) of the t(3;7;9). Marker 3 may have represented der (14) from the t(x;14).

The remaining three cells also showed the above karyotype with del (17) (p11) (figure).

His clinical condition continued to deteriorate. He died three days after starting combination chemotherapy. At necropsy multiple thick walled abscesses were found along the pancreatic border (probably derived from pseudocysts) and in the small bowel mesentery and retroperitoneum. Lymphomatous deposits were present in the liver but not in the spleen or marrow (effect of chemotherapy)?

A computer search of the literature has shown that although pancreatitis has been reported with a variety of solid tumours, such as carcinoma of the stomach, lung, and tonsil,1 it has rarely been found with lymphoma.2 Francis and Glazer reported direct pancreatic disease with Burkitt's lymphoma, but in other cases of tumour associated pancreatitis obstruction to the pancreatic duct was postulated.3 The second patient reported by Anderson et al2 had pseudocyst formation as reported here. The digital gangrene and uveitis remain unexplained; vasculitis was not found at necropsy.

The most common chromosome abnormality in non-Hodgkin's lymphoma is t (14; 18), found in association with follicular lymphoma of follicular centre cell origin. This patient showed a translocation involving chromosome band 14q11. Croce et al postulated that all rearrangements affecting 14q11 in T-lineage malignancies involve the T cell receptor (TCR) chain locus, which is present within this chromosomal band. The del (6) described in our patient has previously been reported in non-Hodgkin's lymphoma.6 We cannot find any cytogenetic details in earlier reports. The combination of clinical features with the cytogenetic findings and T cell origin of this lymphoma seems to be unique.

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Rapid diagnosis of Candida mediasinitis by coagglutination

A rare case of mediasinitis and sepsisemia caused by Candida albicans in a patient who had undergone cardiac surgery was diagnosed sooner by a Candida coagglutination test than by culture findings. The Candida agglutination test had been successfully used by us for the detection of antigenemia in 10 patients with systemic candidiasis, where the coagglutination titres varied from 2 to 54.

In the case reported here, a 28 year old man who had had aortic and mitral valve replacement developed mediasinitis caused by Candida albicans infection. The Candida coagglutination test was extended for the detection of Candida antigen on the first sample of mediastinal fluid received on day 17 after surgery in the laboratory simulaneously, culture was carried out. Both tests were carried out on the second sample of mediastinal aspirate after an interval of 48 hours.

Candida albicans antigen used in the test had been raised in rabbits against whole cell antigen of C albicans serotype A (kindly provided by Dr AA Padhye, Centers for Disease Control, Atlanta) and this serum yielded indirect haemagglutination (IHA) titre of 1:240.1 Cowan I Staphylococcus aureus was grown in Todd Hewitt broth at 37°C, formalin added, and washed as described previously.2,3,4,5,6,7 and used as described by Koshi et al.8 The reagents were prepared by mixing 1-0 ml of 10% Cowan I staphylococcal cells and 0-1 ml of C albicans antigen and incubated at room temperature for 30 minutes. A 2% suspension was satisfactory for the test.

For the Candida coagglutination test the mediastinal fluid was centrifuged at 2500 rpm for 15 minutes. Supernatant (400 ml) was mixed with 20 ml of 2 M sodium hydroxide and heated at 100°C for 30 minutes to remove non-specific reactions, centrifuged at 2500 rpm for 10 minutes, and subjected to the coagglutination test as described previously. Fluid treated with heat and alkali (20 ml) was mixed with 40 ml of 2% Candida coagglutination reagent, as well as coagglutination reagent using Cowan I cells coated with normal rabbit serum (NRS) separately in a ceramic ring VDR slide and rotated for three minutes. The reactions were graded as 4, 3, +, 2, +, 1 and negative based on the formation and size of the clumps and clearing. The coagglutination reaction was considered to be satisfactory when the fluid did not cross react with staphylococcal cells coated with NRS.

To confirm the specificity of the coagglutination reaction a blocking test was carried out by mixing 50 ml of alkali heat treated mediastinal fluid with 50 ml of C albicans antiserum, incubated at 56°C for 10 minutes and then again subjected for the coagglutination test. Patient serum was also treated and tested similarly for Candida antigen, prepared by mixing 1 ml of 0-03 M phosphate buffered saline (pH 7-2), served as positive and negative controls, respectively.

The coagglutination detected mannan antigen and the test results were available one hour after receipt of the specimens. The titre was 64 in the first sample of mediastinal fluid, and a significant increase in titre to 256 was shown in the second sample. The serum also had a high coagglutination titre of 64, confirming a diagnosis of invasive candidiasis. Budding yeast cells with pseudohyphae were detected in the Gram stained smear. Further confirmation of diagnosis was made by the isolation of C albicans in scanty and heavy growth from the first and second samples of mediastinal fluid, respectively. Repeat blood cultures also yielded pure growth of C albicans. No bacteria were isolated from the mediastinal fluid of blood.

The high antigen titre and increase in the Candida antigen titre in the mediastinal fluid and serum with severe candidiasis was probably indicative of a poor prognosis; the patient died four days after diagnosis. Prolonged treatment with broad spectrum antibiotics probably combined with belated aetiological diagnosis and consequent delay in starting antifungal treatment probably caused the fatality in this patient.

The Candida coagglutination test was a useful adjunct for the detection of Candida antigen in body fluids. The coagglutination test was as specific, evidenced by the absence of a cross reaction with sera obtained from a variety of patients with bacterial and fungal infection as well as rheumatoid factor positive sera.1 The coagglutination test described here is recommended as a simple, cost effective, and specific test for the detection of Candida antigen in serum or body fluids.

Since this letter was written the authors have been informed of the coagglutination test for the detection of Candida antigenemia, first described by Aniywo.9
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_J Clin Pathol_ 1990 43: 695-696
doi: 10.1136/jcp.43.8.695

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