Mast Cell and Eosinophil Interaction in Gastric Carcinomas: Ultrastructural Observations

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Abstract. Background: An increase in the number of mastocytes has been described in some human neoplasms, mainly in gastric and colorectal cancer. Materials and Methods: A case of diffusely infiltrated gastric carcinoma, mainly by eosinophils and mast cells, was studied using light and electron microscopy. Results: Using light microscopy, cell clusters containing one mast cell and one to three eosinophils were found in the tumour stroma. Electron microscopy of this unusual stromal element revealed that mast cells established areas of junctions with eosinophils. Moreover, focal, polarized exocytosis of mast cell granules was found in the areas of junctions with eosinophils. Eosinophils in contact with mast cells showed signs of important in situ activation, such as alterations in the size and number of granules, cytoplasmic vacuoles, and scattered extracellular granules. Conclusion: Our ultrastructural study provides morphological evidence of cross-talk between activated mast cells and eosinophils that may play an important role in the enhancement of host immunity against cancer cells.

Mast cells and eosinophils are bone marrow-derived cells that play a key role in the early and late stages of IgE-mediated allergic inflammation (1,2). It has been suggested that mast cells interact with, and are activated by, eosinophil mediators (3, 4). These interactions can take place during the late and chronic phases of the allergic inflammation, as well as in other inflammatory conditions in which mast cells and eosinophils can be found in close proximity (3, 4).

An increase in the number of mastocytes was described in some human neoplasms, mainly in gastric and colorectal cancer, where these cells were dispersed or formed islets (5-9). Profound knowledge of the morphology and function of mast cells may create new paths for pharmacological therapies. Mounting evidence indicates that mast cells accumulate around tumours and may either promote or inhibit tumour growth depending on the local stromal conditions (10).

This report provides morphological evidence of active interaction between mast cells and eosinophils in the tumour stroma of gastric carcinoma.

Case Report

A 57-year-old man was admitted to our hospital with hematemesis. The history was notable for epigastric discomfort for 3 weeks before admission. Upper gastrointestinal endoscopy revealed a large ulcerated Borrmann type III tumour on the lesser curvature of the gastric antrum. Biopsies of the tumour demonstrated a diffuse-type gastric carcinoma. Preoperative chest radiography and whole-body computerized tomography showed no metastatic lesions. Partial gastrectomy with regional lymph node dissection was performed. The patient died 12 months after the presentation of his symptoms. No autopsy was performed.

Materials and Methods

In our Department, gastric tumours are routinely processed for both light and electron microscopic observations (6, 7). Briefly, the fragments of fresh tumour tissue were divided into two portions with a sharp razor blade. The first member of the pair was processed for routine paraffin-embedding together with additional tissue samples taken from the tumour as well as from the surgical borders of the specimens. These sections were stained with haematoxylin and eosin (H&E). The second piece of the paired samples was minced into smaller pieces and destined for electron microscopy. This material was fixed in 3% glutaraldehyde in phosphate-buffered solution, postfixed in 1% osmium tetroxide, and subsequently dehydrated in graded ethanol and embedded in Araldite. Semi-thin Giemsa-stained sections were reviewed. Areas selected for study by electron microscopy included those with mast cell and eosinophil infiltration in the tumour. Ultrathin sections were stained with uranyl acetate and lead citrate and examined under an electron microscope (Zeiss EM 109).

Pathological Findings

Surgical pathology revealed a 3.0 x 5.0 cm ulcerated Borrmann type III tumour on the lesser curvature of the gastric antrum. Microscopically, the tumour consisted of a population of
large, poorly cohesive cells with abundant cytoplasm, invading the mucosal, submucosal and muscular layers of the stomach. The surgical findings were pT2, N2, M0, Stage IIIa according to the TNM system. Neoplastic cells were characterized by large vesicular nuclei with single large nucleoli (Figure 1). The inflammatory reaction mainly comprised eosinophils. Mast cells were found in clusters containing one mast cell and one to three eosinophils (Figure 1).

Electron microscopy revealed areas of intimate contact between mast cells and eosinophils (Figure 2). These cells delimited an intercellular space, where focal degranulation of mast cells could take place (Figures 2-4). This process was evident from the loss of several subjacent granules with residual cytoplasmic lacunae (Figures 2-4). There was formation of small secretory channels and granule opening to the cell exterior (Figures 3-4). Eosinophils in contact with mast cells showed ultrastructural signs of activation such as a reduced number of granules and cytoplasmic vacuolization. A few apoptotic eosinophils were also seen and exhibited condensed chromatin, cytoplasmic vacuolization, and peripheral translocation of granules (Figures 4-5). Clusters of three or more extracellular membrane-bound secondary granules were adjacent to apoptotic eosinophils (Figure 6).

**Discussion**

Occasionally, an ordinary gastric adenocarcinoma exhibits an unusual stromal response, including a massive infiltration of eosinophils, neutrophils or lymphocytes (11). In our case, clusters containing one mast cell and eosinophils constituted an unusual stromal reaction. Electron microscopy showed that mast cells established areas of junctions with eosinophils. We ruled out the possibility that this association was casual, because a focal exocytosis of mast cell granules appeared to be polarized toward the area of junction with the eosinophils. These ultrastructural observations suggest the presence of a cross-talk between mast cells and eosinophils in the tumour stroma.

Focal exocytosis was characterized by the opening of single granules to the cell exterior and/or fusion of a few granules into small secreting channels (12). Two basic patterns of mast cell degranulation have been identified: anaphylactic and piecemeal (13). Anaphylactic degranulation is characterized by extensive fusion of granules with each other and with the plasma membrane, giving rise to open secretory channels which allow the release of granule contents into the local extracellular environment (13). Piecemeal degranulation is characterized by the loss of dense granule materials and the retention of granule containers in the cytoplasm, without membrane fusion events and granule opening to the cell exterior (13). Focal exocytosis may be considered an intermediate pattern of mast cell degranulation between anaphylactic degranulation and piecemeal degranulation, because there is continuity between the mast cell secretory events and these two basic degranulation pathways (12).

Experimental studies have shown that mast cells enhance the cytotoxic activation of mainly peritumoral macrophages and eosinophils and may indirectly exert a cytotoxic effect on cancer cells (10). Tumour stroma mast cells and/or eosinophils have generally been associated with improved prognosis in a wide variety of epithelial neoplasms (5, 14, 15). In our case, eosinophils in contact with mast cells showed ultrastructural signs of activation, including alterations in the size and number of granules, cytoplasmic vacuoles and numerous free granules in the extra-cellular space. Ultrastructural evidence for release of major basic protein-containing crystalline cores of eosinophil granules suggests cytotoxic potential in tumour tissue (16). From these results, we suggest that mast cells may play an important role in the enhancement of local stromal reaction against cancer cells through an indirect mechanism involving adjacent eosinophils.

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Figure 2. Mast cell (M), eosinophil (E), tumour cell (T) and a long cytoplasmic process of fibroblast-like cell (F) delimit an intercellular space, where focal exocytosis of single mast cell granules is noted. x10,000.

Figure 3. Extensive interdigitating plasmalemmal folds were observed on the surface of mast cells in contact with eosinophils (arrow) x20,000.

Figure 4. Mast cell in contact with eosinophil shows evidence of focal exocytosis. Intracellular channels, containing altered cytoplasmic granules, are present. x12,000.
References


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