

Nasopharyngeal carcinoma case with glutathione-S-transferase- π positivity by immunohistochemistry

HASAN ÜSTÜN¹, MELEK ÜSTÜN², GÜLTEN KARPUZOĞLU³,
BURHAN SAVAŞ⁴

Departments of ¹Internal Medicine and ²Pathology, Kocaeli University Medical Faculty, İzmit-Turkey, Departments of ³Pathology and ⁴Internal Medicine, Akdeniz University Medical Faculty, İzmir-Turkey

This report describes a case of stage IV undifferentiated nasopharyngeal carcinoma with glutathione S-transferase- π positivity shown in the lymph node metastasis by immunohistochemistry. Chemotherapy resistance is a major problem in the treatment of patients with nasopharyngeal carcinoma and glutathione S-transferases contribute to the resistance. Detection of glutathione S-transferase- π positivity by immunohistochemistry may affect therapy modalities in chemotherapy resistant cases. [Turk J Cancer 2000;30(2):86-88]

Key words: Nasopharyngeal carcinoma, glutathione-S-transferase, chemotherapy resistance

Resistance to chemotherapeutic agents is a major problem in the treatment of patients with nasopharyngeal carcinoma (1). Glutathione S-transferases (GST) are a family of enzymes produced by several genes. GSTs have been divided into a number of subclasses, alpha, mu, pi and theta. Recent studies have indicated that GST- π may play an important role in the resistance of cancer cells to particular chemotherapeutic agents (2,3).

We describe herein a case of nasopharyngeal carcinoma in which GST- π positivity was shown immunohistochemically.

Case Report

A 51-year-old man was admitted to the hospital with right-sided swelling of the neck on January 1995. Physical examination revealed multiple right cervical lymphadenopathies, the largest four cm in diameter. The lymph node and nasopharynx biopsies were reported as epithelial tumor metastasis and undifferentiated nasopharyngeal carcinoma, respectively. Thoracal and pelvic bone metastases were detected scintigraphically and palliative radiotherapy was given. Six courses of cisplatin and 5-fluorouracil were given and partial response was obtained.

The patient was admitted to the hospital due to recurrence of neck mass on December 1995. Karnofsky performance status was 40%. Biopsy taken from the right supraclavicular lymphadenopathy was reported as undifferentiated carcinoma metastasis. Immunohistochemically, GST- π (GST- π monoclonal antibody-DAKO) positivity in tumor cells was shown (Figure 1). We planned to give chemotherapy with etachrynic acid but because of the patient's poor Karnofsky score, this could not have been done. The patient died in February 1996.

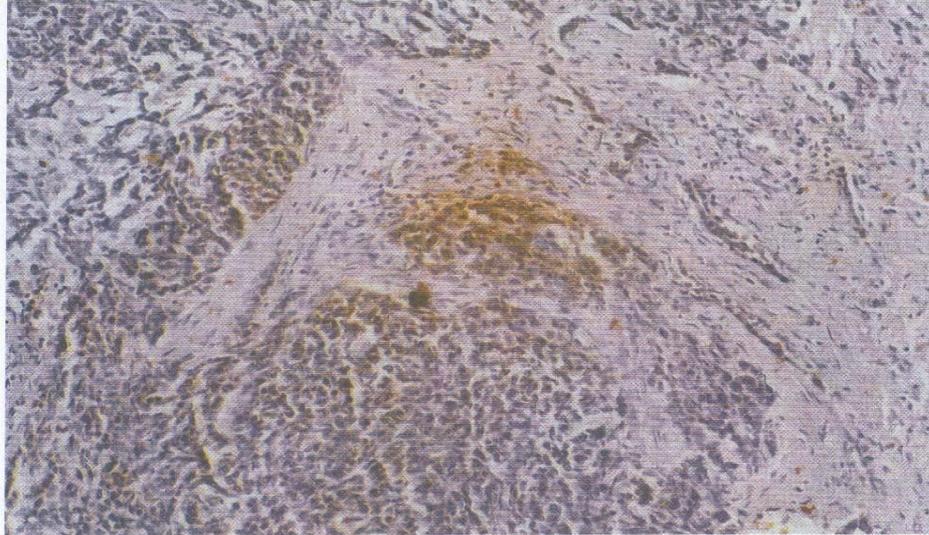


Fig 1. Glutathione-S-transferase- π positivity in the cytoplasm of the nasopharyngeal carcinoma cells (X20) (GST- π monoclonal antibody-DAKO)

Discussion

Glutathione and its associated enzymes are important intracellular antioxidants and serve a protective role within the cell. Glutathione's conjugation with a compound, either spontaneously, or when catalysed by GST, renders the compound less toxic against cellular targets and more hydrophilic and thus more readily excretable (2,3).

Tanita *et al.* (4) reported that GST- π was positively stained in 66.2% of cases with squamous cell carcinoma of the pharynx. GST- π positivity rates for moderately and well differentiated carcinomas were reported as 69.7% and 88.0%, respectively. Thus, GST- π expression seems to be related to the degree of differentiation.

Cisplatin, bleomycin and fluorouracil are effective chemotherapeutic agents in metastatic and/or recurrent undifferentiated nasopharyngeal carcinoma (5). Six courses of cisplatin and 5-fluorouracil regimen were given to the patient. The tumor recurred in five months after chemotherapy. Chemotherapeutic agents such as doxorubicin, BCNU, chlorambucil, cisplatin, cyclophosphamide, mitomycin C, vincristine are affected by GST- π activity (3). We aimed to assess any drug resistance related to GST-p in this case. So

immunohistochemical examination was done and GST- π positivity was seen in tumor cells.

Nishimura et al. (6) reported a correlation between expression of GSTs determined by immunohistochemistry and clinical response to platinum-based chemotherapy in 51 patients with head and neck cancer. The overall response rate (complete response + partial response) for patients with low GST scores was 88% (21 of 24), whereas among the patients with high GST scores, the overall response rate was 19% (6 of 32; $p=0.001$). Patients with a low GST score were 4.7 times more likely to respond to chemotherapy than patients with high GST scores. Among 33 patients treated with chemotherapy for relapsed disease, the overall response rate for patients with low GST scores was 70% (7 of 10), whereas among the patients with high GST scores, the overall response rate was 8.6% (2 of 23; $p<0.001$). They concluded that GST expression correlates well with response to platinum-based chemotherapy in head and neck cancer. So treatment failure in our case might have been resulted from tumor cells with positive GST- π .

Modulators of glutathione levels and of GST enzyme activity are being tested in the clinic as a means of controlling these factors. These substances are L-Buthionine-S-sulphoximine (7), sulphasalazine (8) and etachrynic acid (9). So immunohistochemical GST- π assessment in tumor cells should be used to modify the chemotherapy regimens and the use of inhibitors to modulate GST activity during chemotherapy is a promising strategy in the management of cancer.

References

1. Fandi A, Altun M, Azli N, et al. Nasopharyngeal cancer: epidemiology, staging and treatment. *Semin Oncol* 1994;21:382-97.
2. Salinas AE, Wong MG. Glutathione S-transferases: a review. *Curr Med Chem* 1999;6:279-309.
3. O'Brien ML, Tew KD. Glutathione and related enzymes in multidrug resistance. *Eur J Cancer* 1996;32:967-8.
4. Tanita J, Tsuchida S, Hozawa J, et al. Expression of glutathione S-transferase- π in human squamous cell carcinomas of the pharynx and larynx. Loss after radiation therapy. *Cancer* 1993;72:569-76.
5. Boussen H, Cvitkovic E, Wendling JL, et al. Chemotherapy of metastatic and/or recurrent undifferentiated nasopharyngeal carcinoma with cisplatin, bleomycin and fluorouracil. *J Clin Oncol* 1991;9:1675-81.
6. Nishimura T, Newkirk K, Sessions RB, et al. Immunohistochemical staining for glutathione S-transferase predicts response to platinum-based chemotherapy in head and neck cancer. *Clin Cancer Res* 1996;2:1859-65.
7. Bailey HH, Mulcahy RT, Tutsch KD, et al. Phase I clinical trial of intravenous L-Buthionine sulphoximine and melphalan: an attempt at modulation of glutathione. *J Clin Oncol* 1994;12:194-205.
8. Awasthi S, Sharma R, Singhal SS, et al. Modulation of cisplatin cytotoxicity by sulphasalazine. *Br J Cancer* 1994;70:190-4.
9. O'Dwyer PJ, LaCreta F, Nash S, et al. Phase I study of thiotepa in combination with the glutathione transferase inhibitor etachrynic acid. *Cancer Res* 1991;51:6059-65.