Spontaneous regression of cervical lymph node metastasis in a patient with mesopharyngeal squamous cell carcinoma of the tongue: possible association between apoptosis and tumor regression

Abstract

Background. We report a case of mesopharyngeal squamous cell carcinoma with spontaneous regression of lymph node metastasis. Spontaneous regression of lymph node metastasis of head and neck carcinoma has not been reported previously. Possible causes of the regression of lymph node metastasis include regression of lymphoctic division transiently inflated by an immunological stimulus, and en-bloc tumor necrosis due to degradation of vascularity, such as thromboembolism and intranodal hemorrhage. However, the patient’s history and repeated imaging analyses suggested that these factors were not responsible for the regression. To clarify the etiology of this rare phenomenon, we investigated the cause of spontaneous regression with analyses of paraffin-embedded sections.

Methods. The frequency of cystic lesions, en-bloc necrotic lesions, and apoptosis of carcinoma were investigated with immunohistochemical analysis, and these features were compared with those in specimens from five other patients with head and neck squamous cell carcinoma.

Results. The present case revealed no tendency towards microscopically confirmed cystic formation or necrosis, but the frequency of apoptosis was significantly higher than that in the other five cases. The apoptotic tendency was not restricted to the lymph node in which spontaneous regression was confirmed clinically, but was also consistently observed in other lymph nodes and in the primary lesion that was detected and radically ablated 2 months after complete neck regional dissection had been done.

Conclusion. Our case may be the first case of squamous cell carcinoma undergoing spontaneous regression in which enhanced apoptosis was demonstrated quantitatively. The findings were considered to contribute to evidence of spontaneous regression in squamous cell carcinoma of the head and neck resulting from enhanced apoptosis.

Key words Squamous cell carcinoma · Metastasis · Lymph node · Spontaneous regression · Apoptosis

Introduction

Spontaneous regression (SR) of malignant disease has been defined as the complete or partial disappearance of a malignant tumor in the absence of any treatment, or in the presence of therapy that is considered inadequate to exert a significant influence on neoplastic disease. Because the criteria for SR differ between authors, determining the exact frequency of SR is difficult. However, SR is probably rare. Only 10 to 20 cases are reported each year, and Cole, who first performed a comprehensive case review with reliable criteria for “true” SR, have estimated that SR occurs no more than once in 60 000 to 100 000 cases of cancer.

We report a case of mesopharyngeal squamous cell carcinoma (SCC) with SR of lymph node metastasis. To our knowledge, SR of lymph node metastasis of head and neck SCC has not been reported previously. Possible causes of SR of lymph node metastasis include regression of lymphoctic division transiently inflated by an immunologic stimulus (lymphadenopathy), and en-bloc tumor necrosis due to degradation of vascularity, such as thromboembolism and intranodal hemorrhage. However, the patient’s history and repeated imaging analyses suggested that these factors were not responsible for the regression. To clarify the etiology of this rare phenomenon, we investigated the cause of SR with analyses of paraffin-embedded sections. The frequencies of cystic lesions, en-bloc necrotic lesions, and apoptosis of carcinoma, which were considered to be possible causes of SR, were investigated with immunohistochemical analysis. In this study, the frequencies of cystic lesions, necrosis, and apoptosis in our patient with SR were compared with find-
ings in five other patients with head and neck SCC treated with resection at our institution. The possible mechanisms of SR in our patient are also discussed.

**Case report**

A 67-year-old man was referred to the Department of Plastic and Reconstructive, Head/Neck, and Aesthetic Surgery at Kyorin University Hospital with swelling of the left side of the neck. The patient had first become aware of the lesion 4 months earlier, and the swelling had been slowly worsening. Fine-needle aspiration biopsy performed at a neighboring clinic 3 weeks before the first consultation at our department had suggested class V cytology. Physical examination revealed hard movable masses on the left side of the neck. Ultrasonography (US) visualized several nodes corresponding to the movable masses. The dimensions of the largest mass, located in the jugular chain lymph node region, were $4.0 \times 3.0 \times 2.5$ cm. A primary malignant tumor was not found in the head and neck region despite numerous examinations, including fiberoptic endoscopy. Malignant lymphoma or primary unknown lymph node metastases were suspected. Open biopsy, with possible neck dissection, and rapid pathological diagnosis with frozen sections were planned. On the fourth day after the first consultation, the largest node had spontaneously decreased to $3.4 \times 2.2 \times 1.6$ cm on magnetic resonance imaging (MRI). On the seventh day, palpation showed that the largest node had spontaneously decreased in size. The node measured $3.4 \times 2.3 \times 1.5$ cm on US (see Fig. 1). No cystic or en-bloc necrotic lesions were observed on US or MRI. Clinically, no episodes indicating inflammatory events were noted either subjectively or objectively and no medications such as antibiotics or anti-inflammatory drugs were prescribed during this time period. No other imaging studies using X-rays, such as computed tomography (CT) or positron emission tomography (PET) were performed preoperatively.

On the twenty-ninth day, surgery was performed with the patient under general anesthesia. Metastatic carcinoma was indicated by the findings of frozen-section examination, so a complete neck regional dissection was performed. The reduced lymph node measured $2.9 \times 2.2 \times 1.8$ cm (Fig. 2). The pathological diagnosis was metastatic SCC to the cervical lymph nodes. The node with SR did not show intranodal cystic necrosis (Fig. 2A), although tiny small areas of central necrosis were seen in some cancer nests (Fig. 2B). On the other hand, apoptotic cancer cells were frequently observed (Fig. 2C). Prudent follow-up was continued postoperatively. Two months after the surgery, the primary lesion was detected, with a combination of PET and CT, in the root of the tongue. The lesion was radically ablated and irradiated postoperatively, with no signs of recurrence for 10 months.

**Materials and methods**

**Tissue samples**

Samples of the SR metastatic lymph node and other lymph nodes were obtained from the resected specimen at the initial surgery. The sample of the primary lesion in the root of the tongue was obtained at the second operation. Also, samples from five patients with SCC recently treated with surgery at our institution were collected for comparison (H&E-stained sections of metastatic lymph nodes and a primary lesion showing clinical manifestations similar to those in the present patient). The details of the patients are described in Table 1.

**Histologic analysis and immunostaining**

The specimens for histologic analysis were fixed at room temperature in a 20% formaldehyde solution and embedded in paraffin. To investigate the frequency of apoptosis in...