CLINICAL VALUE OF SERUM SQUAMOUS CELL CARCINOMA ANTIGEN IN THE MANAGEMENT OF SINONASAL INVERTED PAPILLOMA

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Abstract: Background. Although sinonasal inverted papilloma (IP) is a rare benign tumor, it has a tendency to recur and is sometimes associated with squamous cell carcinoma (SCC). Therefore, postoperative long-term follow-up of these patients is recommended. We previously reported that serum SCC antigen might be a useful tumor marker for sinonasal IP. In this study, we investigated whether serum SCC antigen level has a correlation with disease status and is useful in the early detection of recurrent disease.

Methods. Blood samples for the analysis of serum SCC antigen were taken from 28 IP patients before and after surgical treatment.

Results. Twenty-five (89%) of 28 cases showed evaluated serum SCC antigen levels above the upper limit. This marker level decreased in all cases after surgical resection. Four of these patients had a recurrence. None of the patients with recurrent tumor showed symptoms at the time of detection of their recurrent tumor, and recurrence was discovered from elevated levels of SCC antigen.

Conclusions. Serum SCC antigen level has a correlation with disease status of IP and has a potential to serve as a useful tool for monitoring the course of disease. SCC antigen is a reliable tumor marker in the management of sinonasal IPs.

Keywords: squamous cell carcinoma antigen; inverted papilloma; sinonasal tract; tumor marker

Inverted papilloma (IP) is a proliferative lesion of the squamous epithelium lining the sinonasal tract. This tumor is histologically composed of markedly thickened, well-differentiated columnar or ciliated respiratory epithelium with variable squamous differentiation. Although IP is a rare benign tumor (representing 0.5% to 4% of all nasal tumors), it can invade the lacrimal system, the orbit, or the intracranial cavity and can destroy bone and soft tissue. In addition, it has a tendency to recur and is sometimes associated with squamous cell carcinoma (SCC).
Therefore, postoperative long-term follow-up of these patients is recommended. In general, patients are examined postoperatively with nasal endoscopy. CT or MRI is restricted to those areas where nasal endoscopy does not afford adequate visualization. However, it is sometimes difficult to diagnose recurrent disease.

Serum tumor markers have been shown to be helpful in clinical practice to monitor the response to treatment and to indicate recurrent disease mainly in malignant neoplasms. In a previous study, we reported that serum SCC antigen may be a tumor marker for sinonasal IP.

SCC antigen was first isolated biochemically from SCC tissue of the uterine cervix and is transcribed by two highly homologous genes, SCCA1 and SCCA2. The serum SCC antigen is produced mainly by SCCA1. These genes encode for members of the high molecular weight serine protease inhibitor (serpin) family. Serum levels of this antigen in the patients with gynecologic, head and neck, lung, and esophageal SCCs are elevated, and it has been widely used as a tumor marker against SCC. However, serum levels of this antigen have also been reported to be elevated in benign diseases. We also demonstrated that SCCA1 protein is overexpressed in IP tissues and that serum SCC antigen levels are elevated in patients with sinonasal IP.

The aim of this study was to evaluate the clinical usefulness of serum SCC antigen in the follow-up of patients with sinonasal IPs. We investigated whether serum SCC antigen level correlates with disease status and is useful in the early detection of recurrent disease.

**MATERIALS AND METHODS**

**Patients.** Seventeen patients (13 males and four females) with IP who were treated between 1985 and 2000 at the Department of Otorhinolaryngology of Kyushu University, the Division of Head and Neck of the National Kyushu Cancer Center or Department of Otorhinolaryngology of National Kyushu Medical Center, in addition to 11 published cases of IP, were entered in this study. The age of patients ranged from 7 to 83 years old (median, 63.4 years). Extent of disease was staged according to the staging system of Krouse (Table 1) as follows: T1, six patients (21%); T2, 12 patients (43%); T3, 10 patients (36%). For treatment, nine patients (32%) underwent an endonasal endoscopic procedure alone, and 19 patients (68%) were operated on with an open osteoplastic approach combined with a microscopic procedure.

A detailed examination of the resection margins of the primary lesions was carried out for 28 patients, and 25 lesions (86%) were certified to be completely resected. However, one patient had a recurrence. Incomplete resection was documented in three patients, all of whom had a recurrence.

Recent follow-up results were available in all cases. Postoperative follow-up was performed by endoscopic examination and CT or MRI examination. Twenty-four patients (86%) showed no evidence of disease at the end of follow-up, which ranged from 6 to 122 months. Four patients (14%) had a recurrence 4 to 12 months after the initial treatment. All patients with recurrent tumor underwent an endonasal endoscopic procedure alone. The mean postoperative follow-up period was 51 months.

**Evaluation of Serum Squamous Cell Carcinoma Antigen Level.** Blood samples for the analysis of serum SCC antigen were taken from 28 patients with IP before and 2 days after treatment. In addition, the evaluation of serum SCC antigen was also performed every 3 to 6 months after treatment in patients who underwent incomplete resection and/or endoscopic resection alone. None of the patients had any other disease known to

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<th>Table 1. Staging system for sinonasal inverted papilloma (Krouse).</th>
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<td>T1: Tumor totally confined to the nasal cavity. The tumor can involve only one wall of the nose or can be extensive within the nose but must not spread to involve the sinuses or to have extranasal spread on endoscopic and/or CT examination.</td>
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<td>T2: Tumor limited to the medial and superior portions of the maxillary sinus, and/or involving the ethmoid sinus, with or without involvement of the nasal cavity, as noted on endoscopic and/or CT examination.</td>
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<td>T3: Tumor involving the lateral, inferior, anterior, or posterior walls of the maxillary sinus, the sphenoid sinus, or the frontal sinus, with or without involvement of the ethmoid sinus or nasal cavity, as noted on endoscopic and/or CT examination.</td>
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<td>T4: Tumor extending outside the confines of the nose and/or paranasal sinuses to involve adjacent, contiguous structures (eg, the orbit, intracranial compartment, or pterygomaxillary space), as noted on endoscopic and/or CT examination.</td>
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cause elevation of the serum SCC antigen level. We collected blood and obtained serum samples after clotting and centrifugation; the samples were then stored at −20°C. The serum level of the marker was measured in duplicate by a solid-phase immunoradiometric assay. This assay was performed with a commercially available kit (SCC RIA Beads; Abbott Ltd., Tokyo, Japan). Samples were incubated simultaneously with anti-SCC antigen (mouse, monoclonal)–coated beads and 125I labeled anti-SCC antigen. The solid phase and tracer antibodies recognize different epitopes on the SCC antigen molecule. During incubation, both the immobilized antibody and the radiolabeled antibody were bound to SCC antigen, forming a sandwich. The radioactivity bound to the beads was measured in a gamma counter. A standard curve was obtained by plotting the amount of bound radioactivity versus SCC antigen concentrations of the standards. The SCC antigen concentrations of the specimens and controls were run concurrently with the standards and could be determined by the curve. A level of 1.5 ng/mL was taken as the upper limit for normal, representing the 95th percentile in a control group.

**Statistical Analysis.** Statistical analyses were performed with the Student’s t test for paired data. Differences with a p value < .05 were considered significant.

**RESULTS**

Twenty-five (89%) of 28 patients showed elevated serum SCC antigen levels above the upper limit (1.5 ng/mL). The mean level of serum SCC antigen was 3.6 ± 2.5 ng/mL. Serum SCC antigen was elevated in relation to the staging system of Krouse\(^2,3\) (Figure 1). A comparison of serum SCC antigen levels before and 2 days after surgical resection is shown in Figure 2. The SCC antigen level decreased in all patients. There was a significant decrease after surgical resection (p < .0001). Despite surgical resection, serum SCC antigen was above the upper limit for normal in three patients who had incomplete resection. In another patient with recurrent tumor, serum SCC antigen decreased within normal range after...
complete resection and increased again. None of the four patients with recurrent tumor showed symptoms at the time of detection of their recurrent tumor, and recurrence was discovered from elevated levels of SCC antigen (Table 2).

DISCUSSION

Accurate tumor markers are useful for clinicians for the management of tumors. To date, many tumor markers have been reported to be clinically helpful in various malignant neoplasms. SCC antigen has been used for the management of SCC arising in cervical, esophageal, lung, and head and neck region, especially in evaluating therapeutic effects and in monitoring recurrence. However, it is reported that SCC antigen is expressed not only in malignant tumor but also in normal squamous epithelium and is elevated in several benign skin and lung diseases. We also reported that serum SCC antigen was elevated before treatment in patients with sinonasal IP, and SCC antigen was immunohistochemically overexpressed in the squamous epithelium of sinonasal IP tissues.

In this study, we investigated whether serum SCC antigen level correlates with disease status and is useful for the early detection of recurrent disease. As a result, most of the pretreated patients (89%) with sinonasal IP revealed elevated serum SCC antigen levels in relation to staging system. In addition, this marker level decreased in all cases 2 days after resection. Because the serum half-life of SCC antigen is 24 hours, it may be logical to examine the postoperative serum SCC antigen 5 days after resection. However, some patients are discharged from the hospital 2 to 3 days after treatment, and we routinely perform the postoperative blood tests 2 days after operation. There may be a more significant decrease if the postoperative data were examined 5 days after treatment. SCC antigen has been recognized as a tumor marker for patients with SCC. However, in previous studies, the diagnostic sensitivity of SCC antigen for patients with head and neck cancer ranged from 10% to 35%, according to the difference of anatomic sites. The average diagnostic sensitivity of SCC antigen was only 19%. We also reported that SCCA1, which mainly produces serum SCC antigen, was expressed more intensively in sinonasal IP tissues than oral SCC tissues. These results suggest that SCC antigen is a useful tumor marker in detecting sinonasal IPs, although the use of this antigen in patients with head and neck cancer is limited.

IPs are rare benign tumors of the nasal cavities and paranasal sinuses with high recurrence rates and malignant transformation potential. So the objective in treating patients with IP is first complete removal of the lesion without mutilation. We correctly recognized that high rates of recurrence indicate residual disease after incomplete excision. However, it is sometimes difficult to operate completely with an endonasal endoscopic procedure alone and to detect small recurrent tumor during follow-up, because most recurrences are often localized in sites difficult to access. In addition, patients with recurrent tumor often reveal no symptoms. Although CT or MRI is usually performed on those areas where nasal endoscopy does not afford adequate visualization, distinction cannot be made between inflammation and recurrent tumor. Savy et al also reported that it is very difficult to distinguish IP from inflammatory polyps on CT.

The most important role for SCC antigen in the management of IPs is its potential for monitoring the course of disease. In this study, we also evaluated SCC antigen levels in four patients with recurrent tumor. In three of four patients with recurrent tumor, incomplete surgical resection was documented, and serum SCC antigen was above the upper limit for normal after resection. In one other patient with recurrent tumor, serum SCC antigen decreased within normal range after complete resection and increased again. We discovered recurrent tumors from elevated levels of SCC antigen, although none of the patients showed any symptoms at the time of detection of their recurrent tumor. Our data suggested that SCC antigen is also useful in the early detection of recurrent disease.

In conclusion, our results indicate that the serum SCC antigen level correlates with disease status of IP and has a potential to serve as a useful tool for monitoring the course of the disease. SCC antigen is a reliable tumor marker in the management of sinonasal IPs.

REFERENCES