**C-erb-B2 (HER2/neu) EXPRESSION IN SYNOVIAL SARCOMA OF THE HEAD AND NECK**

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**Abstract:** Background. Synovial sarcoma is a malignant mesenchymal tumor composed of varying proportions of spindle and epithelial cell components. Because of the histologic and immunohistochemical similarity of synovial sarcoma to epithelial carcinomas, we hypothesized that the human epithelial growth factor receptor 2 (C-erb-B2, also termed HER2/neu) may contribute to the tumor phenotype and provide a new therapeutic target for this soft tissue tumor.

Methods. Three head and neck, one chest wall, and seven extremity synovial sarcomas were evaluated for C-erb-B2 (HER2/neu) expression by immunohistochemistry, Western immunoblotting, and fluorescence in situ hybridization (FISH).

Results. The head and neck cases demonstrated immunohistochemically strong positive staining, whereas tumors from other anatomic locations showed neither positive nor cytoplasmic restricted staining. Antigen-targeted antibody therapy (trastuzumab) was initiated in two patients.

Conclusions. These results demonstrate that C-erb-B2 (HER2/neu) may play a role in the tumorigenesis of synovial sarcoma; and, therefore, antigrowth factor therapies may provide a previously unrecognized pharmaceutical approach to soft tissue tumors. The data also suggest that although synovial sarcoma of the head and neck and synovial sarcoma of the extremities have similar morphologic features, they may be clinically and mechanistically distinct entities. © 2005 Wiley Periodicals, Inc. *Head Neck* **27**: 883–892, 2005

**Keywords:** C-erb-B2; HER2/neu; synovial sarcoma; trastuzumab

Synovial sarcoma originally specified a group of soft tissue tumors that arise as juxta-articular masses and demonstrate a resemblance to synovial tissue; however, subsequent studies have revealed ultrastructural and immunohistochemical features typical of epithelial differentiation. On the basis of microscopic examination, synovial sarcoma is categorized into three distinct subtypes, including biphasic tumors composed of varying proportions of epithelioid and spindle cells, monophasic tumors composed solely of epithelioid or...
spindle cells, and poorly differentiated tumors composed of intermediately appearing small cells. Compared with other soft tissue tumors, synovial sarcoma is immunohistochemically distinct because of its consistent positivity for epithelial markers such as pancytokeratin (MAK-6), epithelial membrane antigen (EMA), and human epithelial antigen (Ber-EP4). Because of this observation, we hypothesized that the human epithelial growth factor receptor 2 (HER2/neu), also termed C-erb-B2, may play a role in the neoplastic phenotype of synovial sarcoma.

The HER2/neu, encoded by the C-erb-B2 gene, is a Mr 185000 transmembrane glycoprotein (p185*HER2/neu) belonging to a family of four receptor tyrosine kinases that mediate cellular proliferation, differentiation, and survival through the binding of growth factor ligands.1–4 C-erb-B2 (HER2/neu) was originally isolated from an ethylnitrosourea-induced rodent neuroblastoma5 and has subsequently been identified in other human solid tumors, including preinvasive ductal breast carcinomas (60% to 70%), invasive breast carcinomas (25% to 30%), inflammatory breast carcinomas (50%), pancreatic carcinomas (31% to 80%), non-small cell lung carcinomas (13% to 55%), ovarian carcinomas (18% to 43%), endometrial carcinomas (10% to 52%), colorectal carcinomas (33% to 85%), renal carcinomas (22% to 36%), gastric carcinomas (21% to 64%), esophageal carcinomas (10% to 26%), and prostate carcinomas (5% to 46%).5–8 In vitro and in vivo studies have demonstrated C-erb-B2 (HER2/neu) gene amplification and/or protein overexpression to transform murine fibroblasts, induce tumorigenesis, increase metastatic potential, and promote chemoresistance.9–14

Experimental therapies using the recombinant humanized anti-C-erb-B2 (HER2/neu) antibody, trastuzumab (Herceptin; Genentech, San Francisco, CA), have reported reduced cellular proliferation, activated antibody-dependent cellular cytotoxicity (ADCC), and inhibited angiogenesis in strongly C-erb-B2 (HER2/neu)–positive tumors.15,16 Clinical trials have clearly demonstrated a beneficial therapeutic effect when trastuzumab is used as a single agent or combined with multimodality chemotherapy in heavily pretreated patients with refractory breast cancer.17,18 An increased response rate, time to progression, and median overall survival have also been shown when it is combined with doxorubicin or paclitaxel as a first-line treatment of metastatic breast cancer.19 Trastuzumab has also been recently studied in the context of osteosarcoma, another mesenchymal tumor having epithelioid features.20

We evaluated 11 synovial sarcomas for C-erb-B2 (HER2/neu) expression. Three head and neck tumors were strongly positive, whereas one chest wall and seven extremity tumors were negative. Trastuzumab therapy was initiated in two of the positive patients.

**PATIENTS AND METHODS**

**Patients.** Clinical material included biopsy tissue from two patients with radiation- and chemotherapy-refractory synovial sarcoma of the head and neck who concurrently were seen at the University of Nebraska Medical Center (UNMC) Department of Oncology and Hematology in March 2000 (patients 1 and 2). Additional synovial sarcoma cases were obtained by retrospective review of the UNMC Department of Pathology files. One head and neck (patient 3), seven extremity (patients 4–10), and one chest wall (patient 11) tumor specimens were available for further study. Clinical, histologic, cyto genetic, and molecular features are summarized in Table 1.

Patient 1 was a 66-year-old white man with a parapharyngeal mass that was discovered after a 1-year complaint of progressive left ear pain, facial swelling, and dysphagia. Histologic examination of the soft tissue biopsy showed a biphasic synovial sarcoma with predominately epithelial features and a minor spindle cell component. Immunoperoxidase stains demonstrated both cell types to be positive for vimentin, EMA, and MAK-6. Cytogenetics demonstrated the characteristic chromosomal translocation t(X;18)(p11.2; q11.2), and molecular genetics demonstrated the SYT/SSX1 chimeric transcript (Table 1). Numerous complex abnormalities were also identified, including deletion of chromosomes 1, 7, and 9; monosomy of chromosomes 4, 6, and 17; translocation of chromosomes 1 and 11; and an unidentified ring chromosome. Over the course of 5 years, the primary tumor and three recurrent lesions were treated with various combinations of subtotal surgical resection, radiation therapy, and multimodality chemotherapy. On presentation in March 2000 with recurrent disease, the original biopsy specimen and a previously resected lesion from the patient were analyzed for C-erb-B2 expression by immunohistochemistry (IHC) and fluorescence in situ hybridization.
Frozen tumor samples in the UNMC Tumor Repository were also analyzed for C-erb-B2 by Western immunoblot. Trastuzumab therapy was initiated after the positive IHC report (unpublished results).

Patient 2 was a 28-year-old white man with a soft tissue tumor of the left orbit that was discovered after a pathologic skull fracture. Histologic examination showed a monophasic spindle cell synovial sarcoma. Immunoperoxidase stains were positive for vimentin and MAK-6. Cytogenetics demonstrated the characteristic chromosomal translocation t(X;18)(p11.2;q11.2), plus t(10;20) and del 1, 2, 8, and 12. Molecular genetics demonstrated the SYT/SSX1 chimeric transcript (Table 1). Over the course of 14 years, the primary tumor and five recurrent lesions were treated with various combinations of subtotal surgical resection, radiation therapy, and multimodality chemotherapy. On presentation in March 2000 with recurrent disease, two previously resected tumor specimens from the patient were analyzed for C-erb-B2 expression by IHC and FISH. Frozen tumor samples in the UNMC Tumor Repository were also analyzed for C-erb-B2 by Western immunoblot. Trastuzumab therapy was initiated after the positive IHC report (unpublished results).

Patient 3 was an 11-year-old boy with a synovial sarcoma of the pharynx. Histologic review of the slides on file showed a biphasic tumor with predominately spindle cell features and a minor epithelial cell component. Immunoperoxidase stains were positive for vimentin, EMA, and MAK-6. Cytogenetics demonstrated the chromosomal translocation t(X;18), and molecular genetics demonstrated the SYT/SSX1 chimeric transcript (Table 1). IHC and FISH analysis for C-erb-B2 expression was retrospectively performed on archived paraffin-embedded specimens. Frozen tumor samples in the UNMC Tumor Repository were also analyzed for C-erb-B2 by Western immunoblot.

Patient 4 was a 55-year-old woman with a synovial sarcoma of the left forearm. Histologic review of the slides on file showed a monophasic spindle cell tumor. Immunoperoxidase stains were positive for vimentin, EMA, and MAK-6. Cytogenetics demonstrated the chromosomal translocation t(X;18), and molecular genetics demonstrated the SYT/SSX1 chimeric transcript (Table 1). IHC analysis for C-erb-B2 expression was retrospectively performed on archived paraffin-embedded specimens. Frozen tumor samples in the UNMC Tumor Repository were also analyzed for C-erb-B2 by Western immunoblot.

Table 1. Clinical, pathologic, and genetic characteristics of study specimens.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Tumor location</th>
<th>Histologic phase</th>
<th>Predominant cell type</th>
<th>Immunohistochemical features</th>
<th>C-erb-B2 (HER2/neu)</th>
<th>Transcript type</th>
<th>Cytogenetics</th>
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<td>t(X;18)</td>
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<td>NP</td>
<td>NP</td>
<td>t(X;18)</td>
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Note: Immunohistochemical stains were scored as positive (+) or negative (−) for vimentin (Vim), epithelial membrane antigen (EMA), MAK-6, muscle specific actin (MSA), desmin (Des), neuron-specific enolase (NSE), or C-erb-B2 (HER2/neu). C-erb-B2 expression was scored for immunohistochemistry (IHC) as strongly positive (3+), moderately positive (2+), weakly positive (1+), or negative (−). C-erb-B2 expression was scored for Western blot (WB) as strongly positive (3+), moderately positive (2+), weakly positive (1+), or negative (−). C-erb-B2 gene amplification was scored for fluorescent in situ hybridization (FISH) as positive (+) or negative (−). An asterisk (*) denotes data not performed.
the UNMC Tumor Repository were also analyzed for C-erb-B2 by Western immunoblot.

Patient 5 was a 33-year-old woman with a synovial sarcoma of the right foot. Histologic review of the slides on file showed a monophasic spindle cell tumor. Immunoperoxidase stains were positive for EMA. Cytogenetics demonstrated the chromosomal translocation t(X;18). Molecular genetics demonstrated a SYT/SSX chimeric transcript, but the studies were performed before the conventional discovery of SSX1/SSX2 prognostication, so the report did not designate whether SSX1 or SSX2 was involved (Table 1). IHC and FISH analysis for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens. Frozen tumor samples in the UNMC Tumor Repository were also analyzed for C-erb-B2 by Western immunoblot.

Patient 6 was a 48-year-old woman with a synovial sarcoma of the right groin. Histologic review of the slides on file showed a monophasic spindle cell tumor. Immunoperoxidase stains were positive for EMA. Cytogenetics demonstrated the chromosomal translocation t(X;18), and molecular genetics demonstrated the SYT/SSX1 chimeric transcript (Table 1). Immunohistochemical stains for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens.

Patient 7 was a 47-year-old woman with a synovial sarcoma of the right foot. Histologic review of the slides on file showed a monophasic spindle cell tumor. Immunoperoxidase stains were positive for EMA. Cytogenetics demonstrated the chromosomal translocation t(X;18). Molecular genetics demonstrated the SYT/SSX2 chimeric transcript, but the report did not designate whether SSX1 or SSX2 was involved (Table 1). Immunohistochemical stains for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens.

Patient 8 was a 21-year-old man with a synovial sarcoma of the left knee. Histologic review of the slides on file showed a monophasic spindle cell tumor. Immunoperoxidase stains were positive for EMA. Cytogenetics demonstrated the chromosomal translocation t(X;18). Molecular genetics demonstrated the SYT/SSX chimeric transcript, but the report did not designate whether SSX1 or SSX2 was involved (Table 1). Immunohistochemical stains for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens.

Patient 9 was a 77-year-old woman with a synovial sarcoma of the left foot. Histologic review of the slides on file showed a biphasic tumor with a slightly greater spindle cell component. Immunoperoxidase stains were positive for vimentin, EMA, and MAK-6. Cytogenetics demonstrated the chromosomal translocation t(X;18). Molecular genetics demonstrated the SYT/SSX chimeric transcript, but the report did not designate whether SSX1 or SSX2 was involved (Table 1). Immunohistochemical stains for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens.

Patient 10 was a 22-year-old man with a synovial sarcoma of the left knee. Histologic review of the slides on file showed a biphasic tumor with predominantly spindle cell features and a minor epithelial cell component. Immunoperoxidase stains were positive for vimentin and MAK-6. Cytogenetics demonstrated the chromosomal translocation t(X;18). Molecular genetics demonstrated the SYT/SSX chimeric transcript, but the report did not designate whether SSX1 or SSX2 was involved (Table 1). Immunohistochemical stains for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens.

Patient 11 was a 45-year-old woman with a synovial sarcoma of the midline chest wall. Histologic review of the slides on file showed a monophasic spindle cell tumor. Immunoperoxidase stains were positive for vimentin and MAK-6. Cytogenetics demonstrated the chromosomal translocation t(X;18), and molecular genetics demonstrated the SYT/SSX2 chimeric transcript (Table 1). Immunohistochemical stains for C-erb-B2 expression were retrospectively performed on archived paraffin-embedded specimens.

This study was reviewed by the UNMC Institutional Review Board and approved as protocol #003-03-EX.

**Immunohistochemical Staining for C-erb-B2 (HER2/neu) Protein Expression.** Automated immunohistochemical staining was performed using a standardized protocol for the Ventana DAB system. Deparaffinized sections of tumor specimens were pretreated in citric acid buffer at 36°C for 60 minutes to retrieve antigenicity. Slides were then rinsed in water, blocked in 2% bovine serum albumin (BSA)/phosphate-buffered saline (PBS) buffer, pH 7.4, at room temperature for 60 minutes and exposed to a 1:400 dilution of the #A0485 anti-HER2/neu antibody (DAKO Corporation, Carpinteria, CA) for 30 minutes. The slides were washed, and immunocomplexes
were visualized by the immunoglobulin enzyme bridge technique using 3,3'-diaminobenzidine tetra-chloride substrate. Sections were weakly counterstained with 0.1% hematoxylin. Concurrent sections were stained with antivimentin antibodies to assess antigen preservation, and appropriate positive and negative control specimens were included to verify antibody reactivity.

The immunohistochemical stains were scored by a five-tier grading system according to the HercepTest protocol (DAKO Cytomation, Carpinteria, CA). A 3+ score, interpreted as a strong positive result, was given when strongly intense complete membrane staining was observed in greater than 10% of tumor cells. A 2+ score, interpreted as a weak positive result, was given when weakly to moderately intense complete membrane staining was observed in greater than 10% of tumor cells. A 1+ score, interpreted as a weak positive result, was given when membrane staining was incomplete or less than 10% of tumor cells. A 0 score, interpreted as a negative result, was given when membrane staining was observed in greater than 10% of tumor cells. A 1+ score, interpreted as a negative result, was given when weakly to moderately intense complete membrane staining was observed in greater than 10% of tumor cells. A 0 score, interpreted as a negative result, was given when membrane staining was incomplete or less than 10% of tumor cells. A score of cytoplasm (cyto), interpreted as a negative result, was given when substrate was only seen in the tumor cell cytoplasm.

**Western Immunoblot Analysis for C-erb-B2 (HER2/neu) Protein Expression.** For Western immunoblotting, protein extracts from frozen tumor specimens archived in the UNMC Tumor Repository (patients 1–5) were prepared by mechanical homogenization in the presence of triple detergent saline (TDS) lysis buffer (1.0% Triton X-100, 0.5% NP40, and 0.1% sodium dodecyl sulfate [SDS]). A previously characterized human breast tumor and the MDA-MB453 human breast tumor cell line were used as a positive control for C-erb-B2 (HER2/neu). The samples were normalized for differences in concentration by Bradford's assay, denatured by boiling for 10 minutes, and analyzed by SDS–polyacrylamide gel electrophoresis (SDS PAGE). Immunoblots were performed as described previously using a 1:100 dilution of the AB-1 rabbit anti-HER2/neu primary antibody (Oncogene Research, Boston, MA) and a 1:1000 dilution of the A-3687 alkaline phosphatase-conjugated goat anti-rabbit secondary antibody (Sigma, St. Louis, MO). Comparative quantitation of immunostaining for each tumor sample was assessed by densitometric analysis of band intensity with the positive control set to 100% and the negative control set to 0% (Kodak Digital Science, Rochester, NY).

**Fluorescence In Situ Hybridization for C-erb-B2 (HER2/neu) Gene Amplification.** Formalin-fixed paraffin-embedded tissues were cut in 5-µm sections and mounted on glass slides (patients 1–3). Deparaffinization, pretreatment, enzyme digestion, and fixation were performed using the Vysis Paraffin Pretreatment Kit (Vysis, Downers Grove, IL) according to the manufacturer's recommended protocol, and FISH analysis was performed using the PathVysion HER-2 DNA Probe Kit (Vysis) according to the manufacturer's recommended protocol. For each specimen, 30 cells were scored each by two independent reviewers for both C-erb-B2 (HER2/neu) (red) and chromosome 17 (green) signals. Amplification was indicated by an increased ratio of the C-erb-B2 (HER2/neu) gene to chromosome 17 copy number.

**RESULTS**

**Expression of C-erb-B2 (HER2/neu) Protein in Synovial Sarcoma, Immunohistochemistry.** Microscopic examination of the primary and recurrent tumor specimens demonstrated the typical morphologic epithelioid and/or spindle cell features of synovial cell sarcoma. Diagnoses were verified by retrospective review of the previous histologic, cytogenetic, and immunohistochemical studies (Table 1).

Patient 1 had a biphasic synovial sarcoma with predominately epithelial cell features. Immunostaining for C-erb-B2 (HER2/neu) in the original specimen and a previously resected recurrent lesion demonstrated a 3+ strongly positive pattern in greater than 50% of all tumor cells, a 2+ moderately positive pattern in most of the remaining tumor cells, and focal areas of negativity (Table 1 and Figure 1A, B). Although both were positive, the epithelial cells stained slightly more intensely than the spindle cells (3+ compared with 2+) (Figure 1). Trastuzumab therapy was initiated after the positive report (unpublished results).

Patient 2 had a monophasic spindle cell synovial sarcoma. Immunostaining for C-erb-B2 (HER2/neu) in two previously resected tumor specimens demonstrated a strongly positive pattern (3+) in most tumor cells and negativity (−) in focal areas (Table 1). Trastuzumab therapy was initiated after the positive report (unpublished results).

Patient 3 had a biphasic synovial sarcoma with predominately spindle cell features. Immu-
nostaining for C-erb-B2 (HER2/neu) in archived tumor specimens demonstrated a moderately positive pattern (2+) in most tumor cells and a strongly positive pattern (3+) in focal areas (Table 1). Although both were positive, the epithelioid cells stained slightly more intensely than the spindle cells.

Patients 4 through 8 had monophasic spindle cell synovial sarcomas of the extremities, patients 9 and 10 had biphasic synovial sarcomas of the extremities, and patient 11 had a monophasic spindle cell synovial sarcoma of the chest wall. Each demonstrated either no positive (−) or cytoplasm restricted (cyto) staining for C-erb-B2 (HER2/neu) expression (Table 1 and Figure 1C). Thus, each non–head and neck synovial sarcoma was interpreted as negative for C-erb-B2 (HER2/neu) expression.

Expression of C-erb-B2 (HER2/neu) Protein in Synovial Sarcoma, Western Immunoblot. As a confirmatory test for C-erb-B2 (HER2/neu) protein expression, Western immunoblots were performed on tumor tissue extracts. Five cases had adequate tumor samples archived in the UNMC Tumor Repository for further study (patients 1–5). A C-erb-B2 (HER2/neu) overexpressing breast carcinoma cell line termed MDA-MB453 was used as a positive protein control (Figure 1E, lane 1). Extracts from the three head and neck tumors (patients 1, 2, and 3) demonstrated strongly positive HER2/neu expression that were each densitometrically scored as 3+ (Table 1 and Figure 1E, lanes 2–4), whereas extracts from the two non–head and neck tumors (patients 4 and 5) demonstrated comparatively weaker HER2/neu protein expression that was densitomet-
Amplification of the C-erb-B2 (HER2/neu) Gene in Synovial Sarcoma. Karyotypic analysis demonstrated a complex genetic profile, including the characteristic translocation t(X;18)(p11.2;q11.2) for all tumors (Table 1). FISH studies were performed on the three immunohistochemically positive cases (patients 1–3) to determine whether C-erb-B2 (HER2/neu) protein expression was associated with gene amplification. In duplicate studies of tumor cells, only two copies each of the C-erb-B2 (HER2/neu) gene and chromosome 17 were identified (Table 1 and Figure 1D).

DISCUSSION

Growth factors represent an attractive therapeutic target because of their strong association with tumor development. The role of C-erb-B2 (HER2/neu) in breast carcinoma is well established, and recent studies have identified its expression in osteosarcoma, chondrosarcoma, rhabdomyosarcoma, and Ewing’s sarcoma. Although the cell of origin for synovial sarcoma is generally assumed to be an undifferentiated mesenchymal stem cell that undergoes a synovial cell differentiation program after transformation, the mechanisms responsible for development of monophasic and biphasic tumors or the variable proportion of spindle cell and epithelial cell types is poorly understood. However, because of the prominent epithelial component, we hypothesized that growth factors such as C-erb-B2 (HER2/neu) may play an important role in the tumor phenotype, and C-erb-B2 (HER2/neu) targeted antibody therapy may have clinical efficacy. Results demonstrated the three head and neck tumors to display a 3+ strongly positive staining pattern by IHC and Western immunoblotting, whereas tumors from other anatomic locations were negative. Trastuzumab was initiated in the two C-erb-B2 (HER2/neu)—positive patients currently being treated by the UNMC Hematology and Oncology service (unpublished results).

Although gene amplification and protein overexpression are closely associated processes, each represents a distinct molecular condition that may occur independently of the other. Our results demonstrated the three head and neck synovial sarcomas to be C-erb-B2 (HER2/neu) positive by IHC and Western immunoblotting but negative by FISH. Other studies have made similar observations, and several publications have emphasized the direct correlation between C-erb-B2 (HER2/neu) gene copy number and protein level. However, alternative mechanisms exist for protein overexpression, including transcriptional activation, RNA processing, and protein stability. Discrepancies between IHC and FISH results are frequently observed in breast carcinoma, and expression of the C-erb-B2 (HER2/neu) protein has been shown to be frequently discordant with its mRNA level. The biomedical significance of these findings has not been determined. Activation of the OB2-1 transcription factor that upregulates C-erb-B2 (HER2/neu) protein expression may be one mediator of this phenomenon. Posttranscriptional mechanisms such as an altered C-erb-B2 (HER2/neu) 5’ untranslated region (5’ UTR) structure that facilitates ribosomal access and enhances cofactor interactions with downstream initiation sites have been demonstrated in tumor cells, and the potential regulation of growth factor receptor processing by posttranslational modifications such as phosphorylation have not been adequately investigated. Also, because synovial sarcoma has been shown to be positive for BCL2 and various other apoptosis-regulating proteins, C-erb-B2 (HER2/neu) may potentiate the cellular effect of these deregulated factors.

Further studies will be needed to determine whether a large percentage of head and neck synovial sarcomas are strongly positive for C-erb-B2 (HER2/neu) expression or whether this was an isolated observation. George et al first reported six cases of non–head and neck synovial sarcoma that were immunohistochemically negative for C-erb-B2 (HER2/neu) expression, and Merimsky et al published an additional 25 cases that were also negative. Recently, Allander et al reported that the epithelial component of five of five biphasic synovial sarcomas and three of 32 monophasic synovial sarcomas were immunohistochemically positive. Nuñez et al have also shown one case of synovial sarcoma from the neck to be C-erb-B2 (HER2/neu) positive.
Consistent with these previous reports, we observed the epithelioid cells to stain more intensely than the spindle cells. However, in contradiction to these same studies, we also observed strong positivity in the spindle cell component of the monophasic (patient 2) and biphasic (patients 1 and 3) head and neck cases. All tumor cells in the non–head and neck monophasic (patients 4–8 and 11) and biphasic (patients 9 and 10) tumors were completely negative. Multiple sections from multiple surgical accessions from each case were reviewed to verify that the positive or negative C-erb-B2 (HER2/neu) expression observed in either cell type was not due to artifact.

The cellular and molecular mechanisms defining the clinical behavior of synovial sarcoma are poorly understood. The characteristic translocation t(X;18)(p11.2;q11.2) and its resulting SYT/SSX1 or SYT/SSX2 fusion transcript are the only well-described findings, with SYT/SSX1 conferring a poorer prognosis. These tumors may arise in any body compartment and develop at any age, but they most commonly affect the lower extremities of young adult men. Only 3% of primary lesions are found within the head and neck region. However, synovial sarcoma of the head and neck has a significantly better prognosis than tumors located elsewhere. Five-year survival rates range from 47% to 82% for head and neck tumors and 36% to 51% for non–head and neck tumors, respectively.

These data suggest that although synovial sarcoma of the head and neck and synovial sarcoma of the extremities have similar morphologic features, they may be clinically and mechanistically distinct disease processes. Our results demonstrated the expression of C-erb-B2 (HER2/neu) only in the head and neck lesions, and each was characterized by the t(X;18)(p11.2;q11.2) chromosomal translocation and the SYT/SSX1 fusion transcript (Table 1). This observation may initially seem paradoxical, because C-erb-B2 (HER2/neu) is generally recognized as a negative prognostic factor associated with metastasis, chemoresistance, and poor outcome in breast carcinoma. However, a different clinical correlation in soft tissue tumors was recently discovered by the positive association of C-erb-B2 (HER2/neu) expression with increased chemosensitivity and prolonged survival in osteosarcoma. The need for improved molecular characterization of soft tissue tumors has also been suggested by Nielsen et al. Despite limited study, two clinical trials of trastuzumab for recurrent and metastatic osteosarcoma have been initiated. The presence of C-erb-B2 (HER2/neu) expression in the three reported cases of head and neck synovial sarcoma strongly suggests that anti-growth factor antibody therapies such as trastuzumab may represent a previously unrecognized therapeutic approach to these tumors. Further investigation will be necessary to determine the role of C-erb-B2 (HER2/neu) in sarcomagenesis and evaluate its potential efficacy as a pharmaceutical target for sarcoma. Additional staining studies with a larger sample and preliminary therapeutic case reports are planned.

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**REFERENCES**


