

Primary Chondrosarcoma of the Head and Neck in Pediatric Patients

A Clinicopathologic Study of 14 Cases with a Review of the Literature

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BACKGROUND. Primary chondrosarcoma of the head and neck in the pediatric age group is rare. The literature contains several single cases and small series; however, to the authors' knowledge, there has been no previous comprehensive larger study to evaluate the clinicopathologic aspects of these tumors.

METHODS. Fourteen cases of chondrosarcoma of the head and neck from patients age 18 years or younger, diagnosed between 1970 and 1997, were retrieved from the Otorhinolaryngic-Head & Neck Tumor Registry of the Armed Forces Institute of Pathology. No secondary sarcomas (radiation-induced or arising in the context of Maffucci disease or Ollier disease) were included. Clinical, radiographic, and histologic features were reviewed and patient follow-up obtained.

RESULTS. The patients included 6 girls and 8 boys ages 3-18 years (mean, 11.8 years). Patient symptoms (nasal stuffiness or discharge, sinusitis, headaches, or a mass lesion) were related to tumor location and were present for an average of 7.2 months. No genetic abnormalities were documented. The tumors most frequently involved the maxillary sinus (n=4), followed by the mandible (n=3), nasal cavity (n=2), and neck (n=2), with 1 each of the nasopharynx, orbit, and base of the skull. The tumors ranged in size from 2.0 to 15.0 cm (mean, 3.1 cm). All tumors were invasive and malignant as determined by radiology and/or histology. The tumors were Grade 1 (n=9), Grade 2 (n=1), or Grade 3 (mesenchymal, n=2; dedifferentiated n=2). All patients were treated by surgery, followed by radiation (n=5) and/or chemotherapy (n=2). Follow-up was available for 11 patients; all were alive (at a mean of 14.8 years), with only a single patient demonstrating evidence of residual/recurrent tumor (at 16.6 years).

CONCLUSIONS. Primary head and neck chondrosarcoma in the pediatric population is typically low grade in the maxillary sinus or mandible. Despite the invasive and high grade nature of some of these tumors, there is an excellent long term prognosis for patients in this age group with tumors in these locations. *Cancer* 2000;88:2181-8. © 2000 American Cancer Society.

KEYWORDS: chondrosarcoma, head and neck, sinuses, nasal cavity, pediatric patients, adolescent, child, treatment, prognosis.

Chondrosarcomas are uncommon malignant neoplasms of cartilage that can occur anywhere in the body but are most commonly found in the long bones and pelvis, with less than 10% occurring in the head and neck. These infrequent head and neck malignancies usually present in the fifth to seventh decades of life, although a younger age at presentation has been suggested. Pediatric patients with chondrosarcoma of the head and neck are rare, with only a handful of case reports and small series (ranging from two to seven patients) in the literature published in English (MEDLINE 1966-

1999). Given the relative scarcity of this lesion in this location and age group and the lack of a comprehensive series to date, we studied a relatively large group of patients in this category and compared their clinical presentations, radiographic findings, pathologic features, treatment protocols, and clinical outcomes with those of the cases reported in the literature.

MATERIALS AND METHODS

Fourteen chondrosarcomas of the head and neck in pediatric patients were identified in the files of the Otorhinolaryngic-Head and Neck Tumor Registry of the Armed Forces Institute of Pathology (AFIP) between 1970 and 1997. We defined pediatric patients as persons age 18 years or younger at the time of initial presentation. These 14 cases were identified in a review of 1947 (0.71%) pediatric benign or malignant tumors of the head and neck region diagnosed during the same time period. Thirteen cases were obtained from civilian sources, including foreign countries, and one case was received from a military hospital (previously reported). The literature published in English was reviewed for all reported primary chondrosarcomas in the head and neck in children age 18 years or younger, from 1966 to the present, for comparison.

Inclusion in this study required the neoplastic proliferation of cartilage to demonstrate unequivocal cytomorphic and architectural evidence of malignancy (destruction of bone or invasion of soft tissue), i.e., chondrosarcoma. A consensus agreement was reached by all authors regarding tumor grade based on hematoxylin and eosin-stained slides, which were available in all cases. We excluded any patients who had received radiation treatment for either a benign or a malignant process (i.e., thymic enlargement, leukemia, or lymphoma) and patients who had secondary chondrosarcoma as part of a syndrome (i.e., Maffucci or Ollier disease).

Materials within the files of the AFIP were supplemented by a review of the patients' demographics, symptoms at presentation, history of previous irradiation, tobacco and/or alcohol use, radiographic findings, surgical pathology, operative reports, and cancer registry records, in addition to written questionnaires from or oral communication with the treating physician(s). This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research. Follow-up data included information regarding the exact location of the primary site, the specific treatment modalities used, and the current status of the disease and patient.

RESULTS

Clinical

The patients included six girls and eight boys. The patients' ages ranged from 3 to 18 years, with a mean age at presentation of 11.8 years. The females had an older average age (16.7 years) at initial presentation than the males (7.0 years), but given the overall number of patients, the statistical significance of this finding could not be determined. Eight patients were white, four were African American, and two were Asian.

Only 1 patient admitted to a history of tobacco use (exclusively cigarettes); but given his age (17 years), it was difficult to determine the impact of tobacco use, given such a short usage interval. While patients with Maffucci or Ollier disease were excluded from consideration by design, as were patients with previous radiation exposure (either therapeutic or environmental), we did have one patient who had developed a radiation-induced chondrosarcoma. Furthermore, no patient had evidence of a cytogenetic abnormality or other associated diseases.

The patients presented with a mass lesion ($n = 7$), occasionally enlarging in size ($n = 2$); nasal obstruction or congestion ($n = 5$); sinusitis ($n = 1$); epistaxis ($n = 1$); headaches ($n = 2$); pain ($n = 2$); changes in vision (photophobia or visual loss) ($n = 3$); proptosis ($n = 1$); hoarseness ($n = 1$); and/or fatigue ($n = 1$). The duration of symptoms ranged from 1 to 60 months, with a mean of 7.2 months. There was no difference in the average length of symptoms among the various anatomic sites.

Radiographic Studies

Radiographic studies were available for 6 of the 14 patients in this review. All had plain X-ray films of the tumors, whereas four had images obtained by advanced techniques, i.e., computed tomography scans and/or magnetic resonance imaging studies. The findings of a lytic lesion with scalloped borders and internal matrix production, consistent with calcification (chondroid matrix) (Fig. 1), was present in all cases.

Treatment and Follow-Up

All patients (100%) were treated with surgical excision; this was either an excisional biopsy or a more radical procedure (Table 1). Three foreign patients were lost to further follow-up. Of the remaining 11 patients, 5 received radiation therapy and 2 patients were treated with chemotherapy. Whereas the tumors involved the orbit in six patients, globe-sparing surgery was accomplished in each, without the removal of the eye. The type of treatment received did not seem to alter the



FIGURE 1. A computed tomography scan illustrates bone destruction with focal calcification in a sinus-based chondrosarcoma.

overall patient outcome, although there were not enough patients in each therapeutic modality to reach statistical significance. In none of the patients was a complete mandibulectomy or maxillectomy necessary to achieve free surgical margins. Postoperative complications were not reported in any of the cases analyzed.

Follow-up ranged from 3.6 to 27.1 years. The overall survival for the patients as a group was excellent, with a mean follow-up of 14.8 years, whatever the patient outcome. Only a single patient has residual/recurrent disease and is alive at last follow-up (16.6 years). This Asian male patient was diagnosed at age 6 years with a Grade 3 posterior neck/vertebral column chondrosarcoma. He was treated with radical surgery and combination adjuvant therapy (radiation and chemotherapy consisting of vincristine and actinomycin D). Due to the nature of the invasive tumor into the cervical vertebral bodies, he still has localized residual/recurrent disease. The remaining 10 patients are all alive without evidence of disease at last follow-up (mean, 14.6 years). There was no difference in overall outcome between patients based on gender, age, anatomic site, or tumor size, although statistical significance could not be reached with the limited number of patients in each category. Overall, none of the patients developed metastatic disease, and only a single patient developed residual/recurrent disease (as described above). These findings yielded a 100% raw survival rate, a 91.9% 5-year disease free survival rate, and a 72.7% 10-year disease free survival rate (2

patients are alive but are not yet 10 years beyond the initial diagnosis).

Pathologic Features

Macroscopic findings

The lesions involved a number of head and neck sites (Table 1). The most frequent anatomic site was the maxillary sinus ($n = 4$), followed by 3 tumors in the mandible. There were two patients each with tumors in the nasal cavity and soft tissues of the neck, respectively, and one each involving the nasopharynx, orbit, and base of the skull. We did not identify any cases of laryngeal chondrosarcoma in this age group in our files. The tumors ranged in size from 2 to 15.0 cm, with a mean of 3.1 cm. The majority of lesions were received as multiple, irregular fragments of mucoid, myxoid, or soft pieces of tissue, but some were more firm, cartilaginous fragments. The fragments were white-gray to pink-tan, with a glistening cut surface.

Microscopic findings

All lesions, in all locations, demonstrated the typical features of chondrosarcoma, with irregular, binucleated, and multinucleated cells found within lacunar spaces. However, the main morphologic feature of chondrosarcoma, destruction of bone, was not observed histologically in all cases due to fragmentation artifact in a few of the specimens. In these cases, the cytologic details and radiologic destructive features were deemed sufficient to make the diagnosis. There was an overall loss of normal cartilaginous architecture, combined with nuclear enlargement, an increased nuclear-to-cytoplasmic ratio, prominent nucleoli (Fig. 2), occasional mitotic figures, increased cellularity, and spindling in the higher grade tumors. The two mesenchymal chondrosarcomas contained small blue cells with scant cytoplasm, mature hyaline-type cartilage, and a hemangiopericytoma-like vascular pattern. The two dedifferentiated chondrosarcomas had a prominent spindle cell component similar to malignant fibrous histiocytoma, adjacent to the hyaline chondrosarcoma. Histologic invasion into the surrounding soft tissue or bone was demonstrated in four cases. There was no appreciable difference in the histologic grade of the invasive component. The cases were graded as previously described. Nine cases were well differentiated, hyaline-type Grade 1 tumors, whereas 1 case was a myxoid-type (Fig. 3) Grade 2 tumor, and 4 cases were Grade 3 (2 were mesenchymal type and 2 were dedifferentiated chondrosarcomas). The margins of resection were free of tumor in all cases except for 2: for Patient 2, involvement of the neck vertebrae prohibited complete resection, and for Patient 13, a craniotomy was performed and complete

TABLE 1
Clinicopathologic Features of 14 Chondrosarcomas of the Head and Neck in Pediatric Patients

Case no.	Age/ gender	Clinical symptoms (duration, mos)	Side/ size (cm)	Exact location	Pathology/ grade	Treatment	Adjuvant therapy	Patient status (yrs)
1	18/F		U/-	Sinuses, orbit	MCHSA/3		n/a	LTF
2	6/M	Mass increasing in size (60)	L/5	Neck, posterior triangle	DCHSA/3	Biopsy	C, R	A, WD
3	7/F	Sinusitis, visual loss (12)	R/-	Nasopharynx, ethmoid, orbit	WCHSA/1	Biopsy, resection	R	A, NED (27.1)
4	16/M	Mass enlarging in size (11)	R/15	Mandible	WCHSA/1	Hemimandibulectomy	U	LTF
5	17/M	Nasal stuffiness, intermittent epistaxis (1)	L/7	Maxillary sinus, nasal cavity	DCHSA/3	Caldwell Luc	R	A, NED (23.0)
6	18/F	Deviated septum (2)	L/5	Nasal cavity, ethmoid, sphenoid	WCHSA/1	Resection	R	A, NED (21.2)
7	18/F	Headaches, orbital pain, photophobia (5)	L/2.8	Base of skull	WCHSA/1	Craniotomy	N	A, NED (14.4)
8	6/M	Lacrimal duct obstruction and sinusitis (12)	R/3	Maxillary and ethmoid sinus, orbit	WCHSA/1	Biopsy, resection	N	A, NED (13.3)
9	3/M	Nasal mass, obstruction, and discharge; eye swelling (18)	R/-	Nasal cavity, maxillary sinus, orbit	MCHSA/3	Biopsy, resection	R	A, NED (13.1)
10	16/F	Mass (9)	R/2	Mandible	WCHSA/1	Partial mandibulectomy	N	A, NED (12.9)
11	16/F	Mass (8)	R/2	Mandible	WCHSA/1	Biopsy	R	A, NED (9.5)
12	14/M	Facial swelling, headaches, nasal discharge, anosmia, watery eye (1)	L/3	Maxillary and ethmoid sinus, orbit	CHSA/2	Ethmoidectomy, antrostomy, curettage	n/a	LTF
13	10/M	Painful, hard neck mass; hoarseness; fatigue (5)	R/10	Neck, base of skull	WCHSA/3	Excision	C	A, NED (3.6)
14	4/M	Proptosis and displacement (2)	R/5.5	Maxillary sinus, orbit	WCHSA/1	Medial maxillectomy	N	A, NED (2.0)

M: male; F: female; U: unknown; L: left; R: right; MCHSA: mesenchymal chondrosarcoma; DCHSA: dedifferentiated chondrosarcoma; WCHSA: well-differentiated chondrosarcoma; C: chemotherapy; R: radiation; LTF: Lost to follow-up; A, WD: alive with disease; A, NED: alive, no evidence of disease.

surgical excision was not achieved. Both patients received follow-up adjuvant therapy.

DISCUSSION

Chondrosarcomas of the head and neck are rare, accounting for less than 5% of all tumors of the head and neck region. Pediatric patients develop head and neck chondrosarcomas with even less frequency, although

a few authors believe that the head and neck region accounts for a higher percentage of chondrosarcomas in children than in adults. In addition, it has been suggested that pediatric patients account for a higher percentage of head and neck chondrosarcomas than adults, especially when this ratio is compared with the ratios for other anatomic sites. In our series, chondrosarcomas accounted for less than 1% of all head and

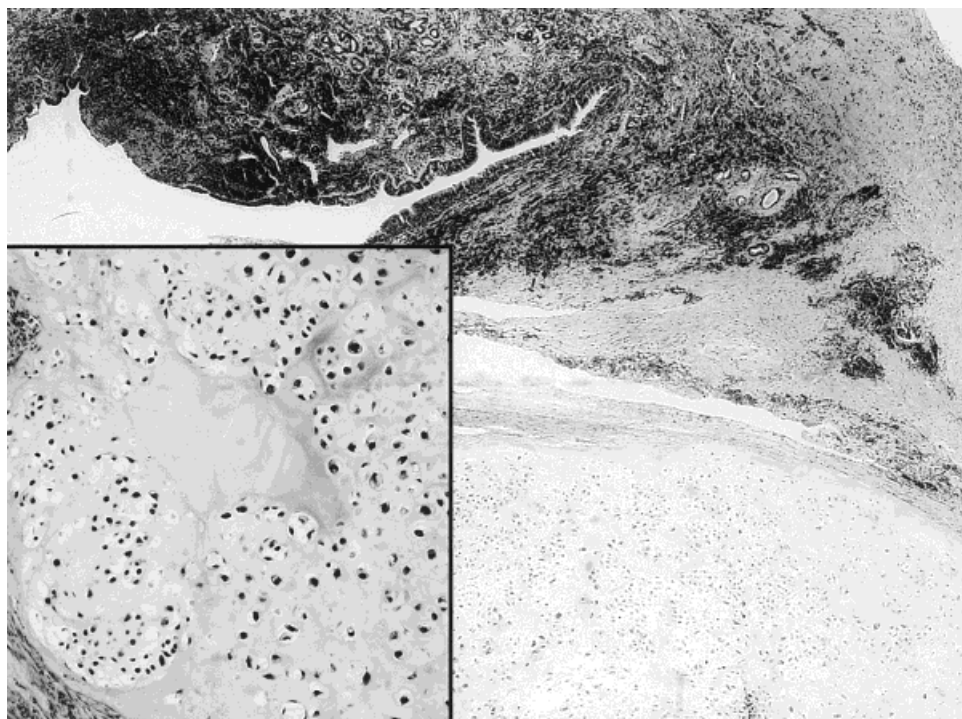


FIGURE 2. Respiratory epithelium is noted overlying the chondrosarcoma. The inset demonstrates high cellularity with nuclear atypia and binucleation.

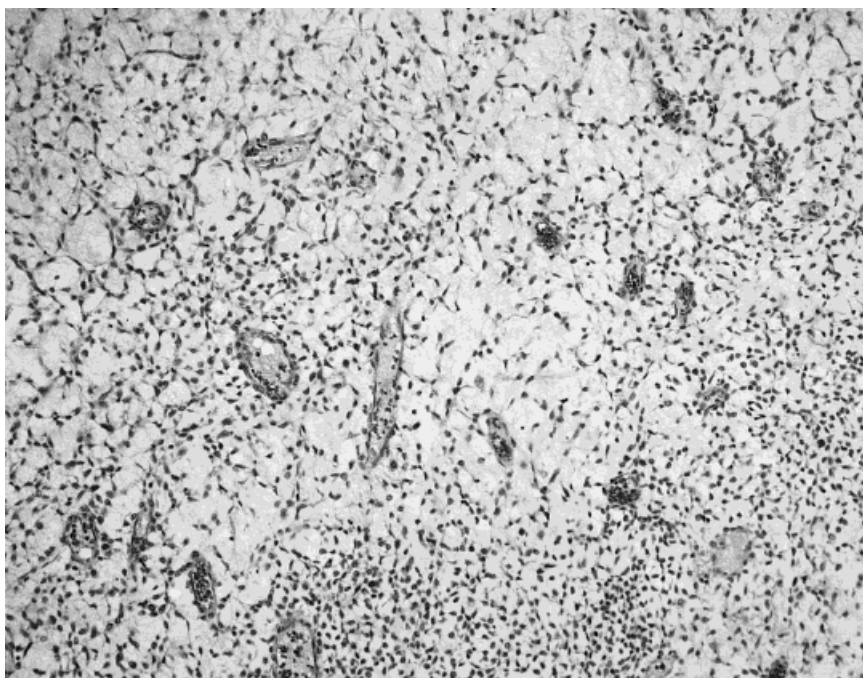


FIGURE 3. An area of myxoid chondrosarcoma demonstrates the characteristic “string of pearls” phenomenon in a tumor that was otherwise a mesenchymal chondrosarcoma.

neck benign or malignant tumors in the pediatric population (birth to age 18 years) of cases reviewed in consultation. In contrast, chondrosarcomas accounted for approximately 2.7% (243 of 9055) of all head and neck benign or malignant tumors in adults. Furthermore, the 14 cases of head and neck chondrosarcomas comprised 4.6% (14 of 307) of all pediatric

chondrosarcomas in all anatomic sites of the body, whereas in adults head and neck chondrosarcomas made up 8.3% (243 of 2935) of all body site chondrosarcomas. Therefore, we were unable to confirm the findings in the literature of an increased percentage of head and neck chondrosarcomas occurring in pediatric patients.

TABLE 2
A Summary of the Literature in English on Head and Neck
Chondrosarcomas in Patients Age 18 Years or Younger^a

All cases ^a	54
Gender	
Female	21
Male	33
Age at presentation	
Range	0.01–18 yrs
Average	12.4 yrs
Girls (average)	13.0 yrs
Boys (average)	11.8 yrs
Duration of symptoms	
Range	0.5–48 mos
Average	13.7 mos
Tumor location	
Right	12
Left	13
Unknown	29
Anatomic site of tumor	
Maxilla alone	15
Nasal cavity and sinuses	8
Sphenoid/Ethmoid/Orbit	5
Nasal cavity alone	4
Orbit alone	4
Nasopharynx alone	3
Nasopharynx and sinus	3
Mandible	3
Neck (vertebrae)	2
Skull (not further specified)	5
Maxilla and sinus	2
Tumor grade	
Grade 1	21
Grade 2	8
Grade 3	14
Unknown	11
Patient outcome	
Alive, no evidence of disease	23 (7.2 yrs)
Alive, locally recurrent disease	9 (4.9 yrs)
Dead, no evidence of disease	1 (5.0 yrs)
Dead of disease	14 (2.2 yrs)
Unknown	6
Evidence of recurrence	23

^a Parameter was not always stated in the report, and therefore the numbers do not necessarily equal the total values in the columns.^{7-9,12,14,17,19-29,40,41}

Our overall findings are similar to the aggregate of those in the literature published in English, although they cannot be compared appropriately with single case reports or with small series of patients, which are typically admixed with adults or non-head and neck lesions (Table 2). There is no appreciable difference in the average age at presentation between our cases (11.8 years) and those in the literature (12.4 years), although we excluded all patients older than 18 years. Our slight male predominance (57.1%) was similar to the cases in the literature (61.1%). We do not have an explanation for this gender difference.

Both our patients and those in the literature presented clinically with symptoms related to tumor location. Similar to our patients ($n = 7$), most patients in the literature ($n = 17$) presented with a mass lesion, followed by nasal obstruction or congestion, and changes in vision (photophobia or visual loss). The patients in our series had a shorter duration of symptoms (7.2 months) than the patients in the literature (13.7 months), but most of the cases in the literature do not specifically state the length of symptoms, and so this figure may be skewed by the references, which document a longer duration of symptoms.

Although there are differences in the specific anatomic sites involved, the maxillary sinus seems to be the most frequent site in both our series (29%) as well as in the literature (33%). There is a variable frequency for the other sites described in our cases and in the literature. We did not find a difference in outcome based on specific head and neck site. Tumor size was not consistently reported, so we cannot comment about the difference between those in the literature and our mean size (3.1 cm).

The majority of our tumors were Grade 1 lesions (64%), similar to the findings in the cases reported in the literature (51%). This is also similar to chondrosarcomas in other anatomic sites in which Grade 1 tumors tend predominate. Dedifferentiated chondrosarcomas were noted in our patients, but perhaps we have a higher number than the literature (2.1%) because of the referral nature of our cases. We had a similar percentage of mesenchymal chondrosarcomas (14% for our series and the literature), which is known to be more common in adolescents than in adults.

Surgery, the initial treatment of choice for patients with chondrosarcomas, was performed on all of our patients and in most of the cases in the literature (Table 2). The use of adjuvant radiation therapy or chemotherapy was employed in 14–36% of cases, without a specific difference noted as to which modality was used more frequently. It has been suggested that chondrosarcomas are not sensitive to radiation therapy or chemotherapy, yet both are still used as adjuvant therapy. It may be that children and adolescents are better able to tolerate such therapy, although we did not specifically study this hypothesis. The number of patients in our series who received adjuvant therapy was insufficient for statistical analysis.

The patients in our series had an excellent long term prognosis, regardless of tumor grade or adjuvant therapy. Overall, 100% of our patients were alive at last follow-up, with only 1 patient demonstrating residual or recurrent disease after 16.6 years of follow-up. This finding is in contrast to the patients in the literature, among whom only 48% were alive without evidence of

disease at last follow-up (mean, 7.1 years), 19% were alive with disease (mean, 4.9 years), and 31% were dead of disease (mean, 2.2 years). None of our patients developed metastatic disease, even though metastases to the lung and bone have been reported in similar cases.^{1,8} The review of the literature extended back to 1966, and it may be that the methods of treatment have changed over the decades, which may account for some of the differences in outcome. Although some authors have suggested that children with chondrosarcoma do less well than adults,^{8,38} the overall 5-year survival for children in the literature is 67%, whereas we report 100% 5-year survival (although it was 91.0% 5-year disease free survival), which is higher than the 50% reported for adults.^{8,30} In addition, it has been suggested that high grade chondrosarcoma histologies do poorly in the head and neck region,^{7,15,30} but we did not find this to be the case in our series.

The lesions in our study contained a significant degree of atypia and cellularity with soft tissue invasion and bone destruction, which are features used to distinguish chondrosarcomas from chondromas and hamartomas. Chondromyxoid fibromas are benign cartilage tumors with associated fibrous and myxoid areas, all of which were absent in our lesions. Osteosarcoma is a malignant tumor with bone formation that may occur commonly in children or adolescents. Although a subcategory of chondroblastic osteosarcoma is known to occur in children, there was no osseous matrix production present directly from the malignant tumor. Areas of reactive bone formation were noted in association with the tumors, but the criteria for the diagnosis of osteosarcoma were not met in these cases. Myxomatous extracellular matrix was observed in the myxoid chondrosarcoma, but this was not the predominant feature. This, coupled with the significant atypia and cartilage production, separated these tumors from myxomas and myxoid sarcomas. The resemblance of a chondrosarcoma, specifically myxoid chondrosarcoma, to a chordoma may be striking, yet chordoma mainly occurs in adults. Furthermore, the strands of larger cells with pink cytoplasm in a wraparound arrangement with aggregated cells in clusters, characteristic physoliferous cells, and keratin immunoreactivity, all support a diagnosis of chordoma. These features were absent in our cases (although we did not perform immunohistochemical studies).³⁹

In summary, children and adolescents can develop chondrosarcomas in the head and neck region, usually involving the maxillary sinus or mandible. The patients will usually present with a mass lesion, although obstructive symptoms, auditory, and ophthal-

mologic symptoms can also be seen. With surgical excision and appropriate adjuvant therapy, pediatric patients will demonstrate an overall good prognosis despite anatomic location, size of the lesion, gender, tumor subtype, or tumor grade. In our experience, these tend to behave as low grade neoplasms in spite of their locally invasive qualities and occasional high grade histology.

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